Defense Health Board

Review of the Scientific Evidence of Using Population Normative Values for Post-Concussive Computerized Neurocognitive Assessments

February 10, 2016

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DEFENSE
HEALTH
BOARD

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MEMORANDUM FOR ACTING UNDER SECRETARY OF DEFENSE (PERSONNEL AND READINESS)

SUBJECT: Review of the Scientific Evidence of Using Population Normative Values for Post-Concussive Computerized Neurocognitive Assessments

The Defense Health Board (DHB) is pleased to submit its report summarizing the findings and recommendations from its independent review of the Scientific Evidence of Using Population Normative Values for Post-Concussive Computerized Neurocognitive Assessments.

On July 25, 2014, the Undersecretary for Personnel and Readiness (USD(P&R)) tasked the DHB to review the scientific evidence for using normative values versus individual baselines for post-concussive computerized neurocognitive assessments. In response, the DHB assigned the Neurological/Behavioral Health Subcommittee to examine the state of the science on computerized neurocognitive testing and develop proposed recommendations for the Board's consideration.

The Subcommittee conducted an in-depth literature review, received briefings from subject matter experts, and conducted panel discussions with leaders in the field of mild traumatic brain injury (mTBI) and neurocognitive testing. Following public deliberation of the findings and recommendations, the attached report was finalized.

On behalf of the DHB, I appreciate the opportunity to provide the Department with this independent review and hope that it provides useful information to further advance health care for our military members.

Nancy W. Dickey, MD

Nancy W. Dickey, MD
President, Defense Health Board

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EXECUTIVE SUMMARY

BACKGROUND

The recent conflicts in Iraq and Afghanistan have raised concerns about the "invisible wounds of war"[1] endured by Service members following deployments. Mild traumatic brain injury (mTBI), also referred to as concussion, is among those injuries and remains difficult to evaluate and manage. The long-term effects of mTBI can leave Service members with insomnia, anxiety, emotional distress, and impaired cognitive functioning. As of March 2015, there have been more than 320,344 diagnosed cases of traumatic brain injury (TBI) (in theater and in garrison) in the U.S. military since 2000.[2] In response to the large number of TBIs, Congress included a provision in the 2008 National Defense Authorization Act (NDAA) stating that the "Secretary of Defense shall develop and implement a comprehensive policy on consistent neurological cognitive assessments of members of the Armed Forces before and after deployment."[3] The Department of Defense (DoD) implemented this requirement through a DoD Instruction that requires all Service members who deploy to undergo baseline neurocognitive testing within 12 months prior to deployment.[4] The Automated Neuropsychological Assessment Metrics 4 (ANAM4), a computerized neurocognitive assessment tool (NCAT) developed by the U.S. Army to assess the cognitive function of Service members, was selected to support this effort. The individual baseline measurements (baselines) obtained using ANAM4 were intended to provide a basis for comparison and evaluation in the event that a Service member experienced an mTBI during his or her deployment. As of September 2015, more than 1.8 million baselines have been completed. An initial normative database (a reference set of baseline tests from the population of interest) was created in 2008 with 107,000 tests stratified by age and sex. There are efforts currently underway to expand the normative database, and to date approximately 1.1 million ANAM4 test results have been selected for analysis and inclusion in the new database.[5]

Given the size of the current ANAM4 database and recent publications indicating that using a normative data set for comparison may be as effective as relying on individual baselines for comparison in assessing cognitive function following mTBI,[6,7] questions have been raised about the utility of continuing to collect pre-deployment baselines. To address these questions, on July 25, 2014, the Undersecretary for Personnel and Readiness (USD(P&R)) tasked the Defense Health Board (DHB) to review the scientific evidence for using population normative values for post-concussive computerized neurocognitive assessments.[8] The DHB Subcommittee on Neurological/Behavioral Health examined the state-of-the-science on neurocognitive assessments and provided recommendations regarding the need for continued baseline testing of individuals, the adequacy of the current normative dataset, the utility of expanding the use of neurocognitive testing beyond the deployment cycle, areas for future research, and the cost-benefit tradeoffs of performing baseline testing.

AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS 4 HISTORY AND USE

The ANAM4 is designed to assess a Service member's cognitive function after he or she has had an mTBI. NCATs are relatively new in the field of mTBI testing. The first computerized NCATs were developed in the late 1980s and were first used in the diagnosis and management of mTBI during the late1990s. Their use has gained popularity in both professional and amateur

sports organizations in addition to their use in pre-deployment baseline testing of Service members.[9]

DoD began developing the ANAM test battery in 1984 to assess the impact of various drugs, medications, and nerve agents on the cognitive performance of Service members.[10] The resulting test battery provided a basis for understanding effects of medication and other environmental factors on the brain, but it was not standardized or well suited for the assessment of long-term conditions. The test battery has since been revised to focus its assessment on the detection and evaluation of neurocognitive deficits that result from mTBI.[10] In theater, clinical guidelines suggest that the test battery be administered if symptoms of concussion are present 24 hours post-injury. This first administration should be completed between 24 to 72 hours post-injury.[11] The test may be re-administered on a regular basis as symptoms resolve to assess for persistent neurocognitive deficits and to inform the return-to-duty decision-making process. A Service member's in-theater post-injury ANAM4 scores may be compared to his or her individual baseline, if available, or to the normative database to determine whether cognitive impairment is present.[12]

ANAM4 plays a specific role in the evaluation and management of mTBI. While valuable as an indicator of cognitive function, it is important to note that the test is only one component of a comprehensive clinical assessment and that test results should be interpreted by a trained neuropsychologist in that context.[13,14]

SENSITIVITY, SPECIFICITY, AND RELIABILITY OF COMPUTERIZED NEUROCOGNITIVE TESTING

Current DoD policy mandates that each Service member complete ANAM4 baseline testing within 12 months prior to deployment. However, recent budget constraints in combination with new research suggesting that normative data may be sufficient to identify impairment in neurocognitive function post-mTBI has prompted a review of the policy and its associated costs.

Comparing the relative effectiveness of individual baseline ANAM4 results and normative data in post-injury assessments is complex. Most experts agree that, logically, a valid high-quality individual baseline would provide the most accurate data for clinicians to make a well-informed return-to-duty decision. However, recent research indicates that collecting an accurate baseline is challenging.[11,15,16] Other elements that must be considered in comparing these two approaches are the value that baseline testing provides for individuals who ordinarily perform significantly above or below the norm; challenges in appropriately interpreting ANAM4 test results; and the size and stratification of the existing military ANAM4 normative database.

> **Finding 1.1:** Current evidence is inconclusive on whether using individual baseline computerized neurocognitive assessment test results is more advantageous, on a population level, than using an optimally stratified normative dataset in evaluating and managing mild traumatic brain injury, including assessing return to duty decision making and prognosis.
>
> **Finding 1.2:** The current ANAM4 military normative dataset is stratified solely by age and sex and does not accurately estimate baseline neurocognitive function in individuals who score at the high or low ends of the scale. Efforts are currently underway to expand

and further stratify this dataset to improve accuracy in estimating cognitive deficits related to mild traumatic brain injury.

Recommendation 1: DoD should continue to analyze existing ANAM4 data to determine whether an optimally stratified normative dataset can be developed that is capable of accurately estimating baseline neurocognitive function, including for individuals who score at the high or low ends of the scale. Specific stratification variables to consider adding include education, rank, standardized test scores, race/ethnicity, and environmental factors such as socioeconomic status.

Finding 2: It is not apparent that an adequate overall assessment of the utility of the current ANAM4 testing program in evaluating and managing mild traumatic brain injury has been accomplished. Moreover, it is not apparent that clinical evaluation and disposition data have been centrally compiled to accomplish this analysis.

Recommendation 2: DoD should analyze current clinical data from mild traumatic brain injury evaluations to determine in what proportion of cases ANAM4 testing provided information of clinical value that was a contributing factor in overall management and disposition of the patient. As part of this analysis, the value of having an individual baseline for comparison should be assessed.

Finding 3: Current evidence is inconclusive regarding the value of routine pre-deployment baseline ANAM4 testing.

Recommendation 3: DoD should request that legislation requiring routine pre-deployment neurological cognitive assessments be rescinded to allow discontinuation of routine pre-deployment ANAM4 baseline testing. DoD should instead conduct prospective research using neurocognitive or other assessment tools to evaluate their usefulness in the management of mild traumatic brain injury and return-to-duty decision-making.

NCATs were designed to track recovery from traumatic brain injury. They were not specifically designed to assess prognosis, and studies have not shown that NCAT test results, including those of ANAM4, are significantly predictive of prognosis following mTBI. However, there is some evidence that better performance on simple reaction time subtests may be indicative of shorter recovery time.[17] Research on clinical cases indicates that loss of consciousness and the length of time that an individual is unconscious following a TBI are correlated with increased recovery time.[18]

Finding 4: ANAM4 testing has not yet been shown to consistently or significantly contribute to assessing long-term prognosis after a mild traumatic brain injury.

Recommendation 4: DoD should analyze post-injury test scores and long-term data documenting the recovery of Service members after a mild traumatic brain injury to determine if post-injury ANAM4 scores consistently or significantly contribute to the assessment of prognosis.

Automated Neuropsychological Assessment Metrics 4 Normative Database and Data Repository

The U.S. military has collected more than 1.8 million baseline ANAM4 test results, which have been incorporated into a searchable database. Test scores for individual Service members are available 24/7 so that clinicians may conduct post-injury evaluations at any time, whether in theater or in garrison. To date, 1.1 million test scores have been deemed suitable for analysis and incorporation into an updated normative database that will be further stratified to improve statistical accuracy in identifying changes in cognitive function when evaluating mTBI with post-injury ANAM4 test scores.[5] Research indicates that demographic factors such as education, rank, ethnicity, and handedness may affect performance on neurocognitive testing and that the creation of norms that reflect these descriptors will improve the accuracy of a normative database.[19,20] Since the characteristics of the military population will likely change over time, efforts should be made to collect and update the ANAM4 baselines to reflect the current demographic distribution of the military population to maintain a current normative database.

Automated Neuropsychological Assessment Metrics (ANAM) Program Costs

As a result of the 2008 NDAA requirement for pre-deployment baselines, the magnitude and costs associated with the ANAM program increased. Licensing and contracting expenses, as well as costs for computers and other infrastructure, increased to accommodate the large number of tests performed on deploying Service members. The overall cost continued to increase through 2011[21] and then began to decrease starting in 2012, correlating with a decrease in the number of troops deployed.[21] DoD currently pays an annual licensing fee to use the ANAM4 tool, as well as a contracting fee that covers testing administration. These costs total approximately $5 million per year.[5] DoD also uses the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) tool to evaluate Service members who are part of the U.S. Military Special Operations units, with an approximate cost of $2 per baseline test and $8 per post-injury test.[22] ImPACT and other NCATs have demonstrated similar accuracy and effectiveness to ANAM4 in evaluating mTBI.[23]

Baselines comprise the vast majority of total ANAM4 tests administered. Post-deployment, clinical, injury, and recovery assessments comprise only 4.6 percent of the total, and tests conducted for unspecified reasons comprise 1.7 percent, indicating that baselines are not accessed for the majority of the population that has undergone testing.[5] Additionally, data provided by the Defense and Veteran's Brain Injury Center show that 80 percent of concussions occur in garrison, where baseline testing is not required, and other neuropsychological assessments may be used for evaluation. In light of the current fiscal environment, as well as the decrease in number of deployments, questions have been raised regarding the cost-effectiveness of the current ANAM program and the continued need for baseline testing.

> **Finding 5:** Currently, there is insufficient evidence to support expanding baseline testing outside of the deployment cycle.

Recommendation 5: DoD should defer a decision to expand ANAM4 baseline testing outside of the deployment cycle until additional research demonstrates that baseline testing improves the evaluation and management of mild traumatic brain injury.

Finding 6: DoD is currently using at least two NCATs (ANAM and ImPACT) to assess neurocognitive function. There are significant differences in the pricing structure for these tools and studies have not shown either tool to have a distinct overall advantage in contributing to the management of mild traumatic brain injury.

Recommendation 6: DoD should conduct a competitive bidding process to select the most cost-effective approach to meet requirements for all non-specialized neurocognitive assessments for the management of mild traumatic brain injury.

AREAS FOR FUTURE RESEARCH

Recent publications outline the need for additional research on the development and appropriate use of NCATs[13,16,24,25]. These tools have become widely used in the assessment and management of mTBI;[14] however, challenges remain in improving their sensitivity, accuracy, and the methodology for interpretation of test results. Areas for future research include cost-effectiveness of baseline testing, accuracy of using baseline versus normative values in assessing mTBI, the development of multimodal assessments methods, validity and accuracy of other computerized neurocognitive assessment tools, test reliability of ANAM4 and its individual subtests, symptomatology of and recovery from mTBI, ANAM4 test score interpretation methodology, and the effect of testing environment on NCAT scores. Of special interest to DoD are new assessments utilizing brain imaging, postural stability, vision testing, biomarkers, and other physiological evaluations. There is increasing evidence that these multimodal assessments, in addition to neurocognitive testing, may provide a more effective approach to the evaluation and management of mTBI.[14,26,27]

Finding 7: There is evidence from academic research and from DoD that multimodal approaches including imaging, use of biomarkers, and physical diagnostic techniques may be more effective than NCATs alone in evaluating and managing mild traumatic brain injury.

Recommendation 7: DoD should sustain and advance research to determine if a multimodal approach can be developed that is cost-effective and superior to NCAT testing alone in assessing and managing mild traumatic brain injury.

Finding 8: Individuals with persistent symptoms following mild traumatic brain injury are often found to have comorbidities such as post-traumatic stress, depression, sleep disturbances, pain, and anxiety. There is insufficient research on the impact of these comorbidities on ANAM4 test performance.

Recommendation 8: DoD should conduct additional research to determine the effects of comorbidities on ANAM4 test performance.

Finding 9: DoD has collected more than 1.8 million baseline, clinical, and other ANAM4 test results.

Recommendation 9: DoD should make a deidentified version of these data available to civilian researchers to leverage those resources in accomplishing additional analyses.

Finding 10: DoD currently administers ANAM4 baseline tests in group settings; however, research indicates that administering computerized neurocognitive tests in a group setting may affect an individual's test score.[28]

Recommendation 10: DoD should determine whether and to what extent the group testing environment affects ANAM4 baseline tests scores as compared to individual ANAM4 testing.

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1. BACKGROUND AND INTRODUCTION

The recent conflicts in Afghanistan and Iraq have brought increased attention to the "invisible wounds" of war[1], such as traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD).[1,29] These invisible wounds can have far-reaching impact, affecting not only Service members, but their families as well.[30] The long-term effects of PTSD and TBI include insomnia, anxiety, emotional distress, or impaired cognitive functioning.[1] These symptoms also affect families, as spouses and children must learn to adjust their behavior and lifestyle to protect and care for the Service member, often causing secondary anxiety.[31] PTSD and TBI can be isolating, leaving Service members and their families disconnected from their regular social activities because of the stress of coping with unpredictable situations. These wounds manifest differently depending on the person, and the medical community still struggles to diagnose and provide effective treatment for these conditions. This report focuses on mild TBI (mTBI), or concussion, and aims to identify the most effective, fiscally responsible approach to using computerized neurocognitive assessment testing in the management of mTBI.

Since the start of Operation ENDURING FREEDOM (OEF) and Operation IRAQI FREEDOM (OIF) the number of diagnosed TBIs has increased as awareness and medical technology have improved.[32] As of March 2015, there have been more than 320,344 diagnosed cases (in theater and in garrison) of TBI in the U.S. military since 2000, and it is assumed that the actual number of TBIs is greater due to a lack of reporting and challenges in identifying subtle symptoms that occur with mTBI.[2] Because of the increasing number of diagnoses and increased focus on these injuries, the Institute of Medicine's Committee on the Assessment of the Readjustment Needs of Military Personnel, Veterans, and Their Families recognized them as the signature wounds of OEF/OIF.[32] Indeed, the high incidence of brain injury among Service members, both deployed and in garrison, has underscored the need for improved diagnosis, treatment, and prevention of TBI.[1]

Mild TBI, commonly referred to as concussion, is defined as "a traumatically induced structural or physiological disruption of brain function as the result of an external force that is indicated by the onset or worsening of at least one of the following clinical signs immediately following the event: loss of consciousness lasting less than 30 minutes; alteration of consciousness or mental state lasting up to 24 hours; posttraumatic amnesia up to 24 hours; or Glasgow Coma Scale (best available score during the first 24 hours) of 13–15."[27] Patients frequently report the sensation of "seeing stars" or having had their "bell rung."[2] Following the acute phase post-injury, symptoms are less distinct and are often attributed to other causes. Headache, dizziness, sleep disturbances, poor coordination, change in mood, and lack of focus frequently manifest; however, individuals may not attribute those symptoms to their injury or choose not to report their symptoms to avoid removal from duty.[33] Even if symptoms appear mild, the brain is vulnerable to repeat trauma following an mTBI. Appropriate management is vital to ensure that Service members who experience mTBI do not place themselves, others, or their mission at risk.[34]

Recognizing the need for improved screening and diagnosis of mTBI, the U.S. Army began research on computerized neurocognitive assessments in consultation with military and civilian experts in 2001.[10] Efforts focused on the Automated Neuropsychological Assessment Metrics (ANAM), a test initially developed in 1984 to assess the impact of various drugs on the cognitive

function of members of the U.S. military.[10] The resulting computerized assessment consisted of a battery of tests intended to evaluate cognitive processing speed, resistance to interference, and working memory. ANAM testing was not broadly implemented in the military until 2008, when, amidst growing concern over the lasting effects of TBI, Congress passed a bill requiring all Service members who deploy to undergo baseline neurocognitive testing within 12 months prior to their deployment.[3] The intent was to ensure that all Service members would have a baseline that clinicians could compare with post-injury or post-deployment ANAM scores to determine whether cognitive impairment was present.

The ANAM, currently in its fourth iteration (ANAM4), consists of 22 modules that are intended to detect changes in cognitive function that occur because of injury, illness, or exposure. A list of the modules is included in Appendix C. Since its implementation in 2008, the ANAM has evolved to incorporate improved measures for effort and validity and further research has been conducted to assess its reliability, sensitivity, and specificity.[6,7,15,36-38] Regulations and guidelines have been developed to aid in its effective application. A 2013 Department of Defense Instruction (DoDI) states that "Neurocognitive assessment tools will be used in a screening capacity to detect cognitive changes as part of a clinical evaluation and will not be used as a standalone diagnostic tool."[4] Currently, the ANAM must be administered within 12 months prior to deployment, but it is not routinely administered following a deployment unless a Service member's post-deployment questionnaire indicates that they may have experienced a TBI while deployed. The Defense Centers of Excellence for Traumatic Brain Injury and Psychological Health has also developed guidelines for the assessment and management of acute mTBI.[12] If a post-injury or post-deployment ANAM is required, the clinician may compare the results of the test to the Service member's baseline to aid in their overall evaluation. This post-injury test is a tool used in conjunction with other assessments and clinical judgment to determine whether a Service member may return to duty.

The current standard for evaluating mTBI is comparing a Service member's post-injury ANAM scores to his or her baseline score. Ideally, this provides a reliable point of reference for the evaluating medical professional to determine whether the Service member shows any decline in cognitive function that might be related to his or her mTBI.[41,42] This comparison may be particularly valuable when making decisions on whether a Service member has recovered to his or her baseline cognitive functioning and is fit to return to duty. While this approach to evaluating mTBI has historically been accepted as the standard of care, obtaining baselines for all deploying Service members is expensive, and the overall impact on clinical decision making is unclear. Some recent publications suggest that comparison to properly stratified normative data may be sufficient to determine whether an individual can return to duty.[7,16] While fiscally advantageous, the use of normative values also has drawbacks. Compared with the use of individual baseline values, using normative values typically reduces the specificity of the ANAM4 in detecting cognitive deficits in individuals.[43]

In the current fiscal environment, the interest in using normative values versus individual baseline values for comparison has increased. As the size of the ANAM data repository has expanded, there may be an opportunity to create a more robust normative database with significantly improved test characteristics. Additionally, since more than 80 percent of TBIs are

diagnosed in garrison, having a more accurate normative database may help avoid the cost associated with obtaining baseline tests in all Service members.[44]

On July 25, 2014, the Undersecretary for Personnel and Readiness (USD(P&R)) tasked the Defense Health Board (DHB) to review the scientific evidence for using population normative values for post-concussive computerized neurocognitive assessments. From July 2007 to July 2014, DoD completed more than 1.5 million pre-deployment baseline ANAM assessments, of which an initial subset of 107,000 comprises the current normative dataset.[8] As of July 2014, there have also been 26,524 post-injury comparison assessments.[5] Given the size of the current data repository and recent publications indicating that using a normative data set for comparison may be as effective as relying on individual baselines in assessing cognitive function following mTBI, questions have been raised about the utility of continuing to collect pre-deployment baselines. To address these concerns, the USD(P&R) requested that the DHB examine the state of the science on neurocognitive assessments and provide recommendations regarding the need for continued baseline testing, the adequacy of the current normative dataset, the utility of expanding the use of neurocognitive testing beyond the deployment cycle, areas for future research, and the cost-benefit tradeoffs of performing baseline testing on deploying Service members.

The Neurological/Behavioral Health Subcommittee of the DHB conducted an extensive literature review, received briefings, and conducted panel discussions with subject matter experts to address the questions outlined in the tasking. The Guiding Principles (listed below) were adopted as a foundation for review of the evidence for baseline neurocognitive testing using the Automated Neurocognitive Assessment Metrics (ANAM) 4.

Overarching Principle
It is the duty of DoD to provide high-quality care to Service members who experience mTBI.

Guiding Principles
These principles require that the changes recommended by the subcommittee, when taken as a whole, must

i. ensure that Service members who experience mTBI receive the best care possible including
   a. prompt and accurate diagnosis of mTBI
   b. accurate assessment of cognitive deficits resulting from mTBI
   c. appropriate recommendations for return-to-duty post-mTBI;

ii. identify the most effective applications of computerized neurocognitive testing in assessing mTBI;

iii. be evidence-based, taking into account the most current research and best practices in DoD, other federal agencies, academia, and the private sector.

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2. AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS 4 HISTORY AND USE

The Automated Neuropsychological Assessment Metrics 4 (ANAM4) is part of a family of neurocognitive assessment tools known as computerized neuropsychological assessment devices (CNADs). The American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology define a CNAD as "any instrument that utilizes a computer, digital tablet, handheld device, or other digital interface instead of a human examiner to administer, score, or interpret tests of brain function and related factors relevant to questions of neurologic health and illness."[45] The Department of Defense (DoD) uses the term "Neurocognitive Assessment Tool" (NCAT) to refer to computerized neurocognitive assessment devices. This report will use the term NCAT to remain consistent with terminology used by DoD. NCATs are widely used to assess cognitive functioning in individuals with conditions that affect their brain function, such as dementia, stroke, lupus, and traumatic brain injury (TBI). Tests that are frequently used to assess mild traumatic brain injury (mTBI) include the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), ANAM4, CogSport, CNS Vital Signs, and HeadMinders.[6,46] These tests rely on similar testing paradigms and demonstrate no significant difference in reliability, sensitivity, and specificity.[6,23]

Experts in the field generally agree that, in theory, having a valid baseline for computerized testing provides the most accurate measurement for comparison when assessing an individual for mTBI,[13] particularly when the baseline and post-injury assessments are performed under similar conditions.[28] A benefit of NCATs is that they allow for accurate, rapid analysis of psychometrics such as simple reaction time and executive function.[13,45] This is particularly useful when patients have a valid baseline test that accurately reflects their neurocognitive function when healthy. While NCATs have improved the ability to more efficiently and accurately assess time-dependent cognitive functions such as simple reaction time, they are only one component of a comprehensive clinical evaluation of mTBI.[13,47] Typically, the evaluating clinician will document the patient's mental and physical symptoms and conduct a thorough survey of the patient's mood, sleep cycle, balance, physical coordination, pain, and cognitive functioning. An NCAT allows the clinician to determine if there is evidence of an objective change in the patient's cognitive function by comparing their post-injury test results with their own pre-injury baseline or with normative data to determine if their function is within the normal range of an appropriate comparison group. These data can provide important insight to an individual's cognitive function; however, the psychometrics measured by NCATs are inherently variable when other factors such as fatigue, stress, and mood are present. As such, a clinician must interpret NCAT scores as part of a broader examination. The frequent presence of comorbidities such as posttraumatic stress disorder (PTSD), sleep disorders, and depression can affect NCAT test results as well, requiring a nuanced interpretation of test results in the greater context of a patient's overall mental and physical health.

Given Terms of Reference (Appendix B) for this report, the discussion will focus on ANAM4 and its use in the military.

2.1 Role of NCATs in Mild Traumatic Brain Injury Evaluation

NCATs are relatively new in the field of concussion testing. The first NCATs were developed in the late 1980s and were initially used in the diagnosis and treatment of concussion during the mid to late 1990s, although their use was not widespread. Over the past several years, their use has gained popularity in both professional and amateur sports organizations in addition to their use in pre-deployment baseline testing of Service members.[9] The National Football League has instituted mandatory baseline testing for its athletes, and many college, high school, and elementary school sports programs have begun to require participation in NCAT programs. In spite of this increased use for mTBI assessment in sports, many clinicians do not use NCATs on a regular basis. A 2014 survey conducted by Rabin et al found that 45.5 percent of clinicians who responded to the questionnaire had never used NCATs, noting that one-on-one interaction with their patients during the administration of traditional neurocognitive testing is beneficial in assessing their mental and cognitive state. Additionally, the survey indicated that 14.1 percent of clinicians used them rarely, 19.6 percent used them sometimes, 18.2 percent used them often, and only 2.6 percent always used them.[48]

While the use of NCATs is increasing, questions remain on the most appropriate way to incorporate their use in assessing mTBI. Although some organizations acknowledge that neuropsychological testing is useful in evaluating mTBI, they note that interpretation of NCAT test results should be done by a health care professional with appropriate training and in the context of a comprehensive clinical exam. Several key sports organizations have published position statements regarding the management of mTBI and the use of computerized testing in making return-to-play decisions. The American Medical Society for Sports Medicine notes the following in its 2013 position statement on Concussion in Sport:

> Most concussions can be managed appropriately without the use of neuropsychological testing…neuropsychological tests are an objective measure of brain-behavior relationships and are more sensitive for subtle cognitive impairment than clinical exam...Computerized neuropsychological testing should be interpreted by healthcare professionals trained and familiar with the type of test and the individual test limitations, including a knowledgeable assessment of the reliable change index, baseline variability, and false positive and false negative rates.[49(Pg. 2)]

Similarly, the 2013 consensus statement published after the fourth International Conference on Concussion in Sport states

> …it must be emphasized, however, that [neuropsychological] assessment should not be the sole basis of management decisions. Rather, it should be seen as an aid to the clinical decision making process in conjunction with a range of assessments of different clinical domains and investigational results. It is recommended that all athletes should have a clinical neurological assessment (including assessment of their cognitive function) as part of their overall management. This will normally be performed by the treating physician often in conjunction with computerised neuropsychological screening tools. Formal NP

[neuropsychological] testing is not required for all athletes; however, when this is considered necessary, it should ideally be performed by a trained neuropsychologist.[14]

2.2 History and Development of the ANAM

Development of the ANAM test battery began in 1984 when a team of DoD neuropsychologists and researchers created a method to assess the impact of various drugs, medications, and nerve agents on the cognitive performance of Service members.[10] The resulting test battery provided a basis for understanding effects of medication and other environmental factors on the brain, but it was designed for the assessment of long-term comorbidities associated with mTBI and post-traumatic stress. The need for a neuropsychological assessment tool was again underscored in the early 1990s when Service members returned home from Gulf War deployments with various, persistent neuropsychological symptoms. The Office of Military Performance Assessment Technology resumed research on the existing testing battery, developing the first iteration of ANAM in 1995. This first version of ANAM was intended to detect changes in cognitive function due to exposure to chemical agents and environmental factors.

ANAM development paralleled similar efforts in the civilian sports sector. Pencil and paper neuropsychological testing had been gaining popularity as a method to monitor and assess neurodegenerative disease in the 1960s, and during the 1970s researchers began studying its use to assess mTBI.[51] Clinicians began to use acute sideline and recovery assessment neuropsychological testing for mTBI in the 1970s when the Colorado Medical Association issued guidelines on concussion management in response to the deaths of two high school football players from head trauma-related complications. It remained a small field until 1986, when Barth et al published a new methodology for assessing sports-related mTBI that relied on baseline testing to determine the extent of the injury and measure recovery. This methodology spurred the development of new neurocognitive tests during the 1990s and drove the growth of the computerized neuropsychological testing industry to assess mTBI in sports, where baseline testing was quickly incorporated into preseason screening and concussion management guidelines. During this surge in mTBI testing technology in the civilian sector, DoD was developing similar technologies tailored to the military population as it created the ANAM testing battery and began to repurpose it for application as a concussion assessment tool.

When substantial numbers of Service members returned from Operation ENDURING FREEDOM (OEF) and Operation IRAQI FREEDOM (OIF) deployments with TBI, there was increased interest in having an effective neurocognitive assessment testing battery. Diagnosis and treatment of these injuries was poorly understood and DoD required a reliable quantifiable method to assess the impact of TBI on the cognitive functioning of Service members before they were allowed to return to duty. Rather than develop an entirely new testing platform, DoD repurposed the ANAM testing battery, updating testing methods for key areas affected by mTBI including mathematical reasoning, simple response time, delayed memory, and spatial reasoning.[10]

Although ANAM was initially developed by DoD, the license for the test battery is currently held by the Center for the Study of Human Operator Performance (C-SHOP) at the University of

Oklahoma. C-SHOP partnered with DoD in researching and developing the computer platform and quality assurance measure for ANAM, and in 2006 DoD sold the license to C-SHOP, allowing it to continue its work on the test library.[50] This arrangement requires that DoD must pay to use the test for its pre-deployment baseline ANAM assessment program. DoD's current TBI assessment program requires DoD to contract with C-SHOP and an external test administration service to conduct the required baseline testing for deploying Service members. The current licensing contract for ANAM4 pre-deployment testing is $1,000,000 for up to 100,000 ANAM4 tests and $140,000 for each additional 20,000 tests.[5] The costs associated with the current ANAM testing policy are further discussed in Section 5.

The ANAM has evolved as researchers have learned more about mTBI. DoD currently uses the ANAM4 Traumatic Brain Injury Battery - Military (ANAM4 TBI-MIL, referred to in the report as ANAM4), a specialized subset of tests and questionnaires from the full ANAM library. The included modules and the functions they assess are shown in Table 1 below.

Table 1. ANAM4 TBI Battery Sub-tests[50]

Module Name	Function
Demographics	User Profile
TBI Questionnaire	TBI History
Sleepiness Scale	Fatigue
Mood Scale	Mood State
Simple Reaction Time	Basic Neural Processing (speed/efficiency, emphasis on motor activity)
Code Substitution – Learning	Associative Learning (speed/efficiency)
Procedural Reaction Time (RT)	Processing Speed (choice, RT/rule adherence)
Mathematical Processing	Working Memory
Matching to Sample	Visual Spatial Memory
Code Substitution – Delayed	Memory (delayed)
Simple Reaction Time (R)	Basic neural processing (speed/efficiency)

Adapted from C-SHOP, 2007, ANAM4 TBI: User Manual.

This selection of tests is intended to measure those cognitive functions thought to be most affected by mTBI. However, the psychometrics used are also inherently variable in humans.[50,52] Factors such as effort, mood, sleepiness, testing environment, stress, and comorbid conditions can influence test results. DoD's ANAM program has several measures in place to control for this during pre-deployment baseline testing. For example, testing facilities are designed to reduce distraction, and exam proctors are trained to review a Service member's responses to the TBI Questionnaire, Sleepiness Scale, and Mood Scale to determine whether he or she should be able to perform at his or her normal level. ANAM4 proctors are also trained to monitor Service members as they take the test to look for signs of sleepiness or lack of effort.[50] In some cases, proctors have the option to run additional analyses on ANAM4 results to identify patterns associated with intentionally low effort or the influence of stress, sleepiness, or other factors.[53] Taken together, these measures support the collection of accurate test results and valid baselines.

Another significant influence on test scores is the practice effect, a "gain in score on cognitive tests that occurs when a person is retested on the same instrument, or tested more than once on

very similar ones."[54] If a Service member has taken the ANAM4 multiple times, their score may increase because of practice effects, possibly affecting the diagnostic utility of the test. A study conducted by McCrea et al showed that, while the impact is small, practice effects do affect test scores in both injured and uninjured athletes when computerized neurocognitive tests were administered serially after mTBI to assess recovery progress. Practice effects were smaller in acutely injured athletes than in uninjured athletes, but the effects increased when tests were administered repeatedly within a short period of time.[25] NCATs aim to minimize the impact of practice effects on serial test administrations through the development of multiple test forms to reduce predictability of the test.[50]

2.3 DoD ANAM Testing Policy/ Application of ANAM

The current DoD policy for neurocognitive testing was established in 2008 in response to congressional mandate, outlined in Section 1673 of the National Defense Authorization Act (NDAA) HR 4966. The law states "the Secretary [of Defense] shall establish… a protocol for the pre-deployment assessment and documentation of the cognitive (including memory) functioning of a member who is deployed outside the United States in order to facilitate the assessment of the post-deployment cognitive (including memory) functioning of the member. [The protocol] shall include appropriate mechanisms to permit the differential diagnosis of traumatic brain injury in members returning from deployment in a combat zone."[55] The law also states that the Secretary of Defense shall ensure the implementation and evaluation of up to three pilot projects to obtain pre-deployment baselines to determine the best method of baseline collection and post-deployment mTBI assessment. ANAM was chosen to fulfill this requirement, and starting in 2008 all deploying Service members were required to undergo baseline neurocognitive testing within 12 months prior to deployment. The baselines obtained from this program are stored in a data repository for access if a Service member experiences mTBI in the field or reported past mTBI when completing the post-deployment questionnaire.

As the ANAM testing program matured, additional DoD Instructions and Directive Type Memorandums outlining standard procedures, training, and courses of action in the identification and treatment of TBI and mTBI were developed to further improve the TBI system of care.[56,57] These guidelines outline steps for the medical management of mTBI and stress the importance of neurocognitive testing in assessing the extent of the injury and measuring progress in recovery post-injury. The current DoD policy on neurocognitive assessments, described in DoD Instruction Number 6490.13, states:

> Neurocognitive assessment tools will be used in a screening capacity to detect cognitive changes as part of a clinical evaluation and will not be used as a standalone diagnostic tool. The Automated Neuropsychological Assessment Metrics (ANAM) is the DoD-designated neurocognitive assessment tool to support this instruction. The use of the this tool will remain in effect until such time as evolving science and medical best practice guidelines inform a change in policy.[58]

As stated above, the requirements of the 2008 NDAA are in place, and every Service member who deploys undergoes baseline testing within 12 months prior to deployment. The baselines are maintained in the ANAM data repository and clinicians may request access to a Service

member's baseline in case a post-injury or post-deployment ANAM comparison is required. When Service members redeploy, ANAM is not administered unless there is indication that they may have sustained an mTBI while deployed. The ANAM baseline assessment must be re-administered prior to a subsequent deployment if it has been more than 12 months since the previous baseline was established.[4]

ANAM4 may be used in different ways to monitor recovery after an mTBI. In theater, clinical guidelines suggest that the test battery be administered if symptoms of concussion are present 24 hours post-injury. This first administration should be completed between 24 to 72 hours post-injury.[11] The test may be re-administered on a regular basis as symptoms resolve to assess for persistent neurocognitive deficits and inform the return-to-duty decision-making process. A Service member's in-theater post-injury ANAM4 scores may be compared to their individual baseline, if available, or to the normative database to determine whether cognitive impairment is present.[12]

The U.S. Naval Academy (USNA) applies a different methodology in its use of ANAM4. All students at USNA, referred to as midshipmen, undergo baseline neurocognitive testing with a version of ANAM4 utilizing additional subtests for executive function, visual spatial processing, and working memory. In addition, a built-in effort measure is used to assess test validity. When midshipmen experience mTBI, they are removed from normal activity until their symptoms completely resolve. Post-injury ANAM4 testing is administered when the student is symptom free, including after physical exertion. If a midshipman's ANAM4 score remains significantly below baseline after physical symptoms have resolved, he or she will be referred for additional testing to guide further treatment and recovery.[53]

The two approaches listed above for using the ANAM4 to inform return-to-duty decisions embody significant differences in the perceived value of baseline testing. The first approach, applied in theater, aims at documenting the occurrence of mTBI and measuring acute cognitive impairment as part of the larger clinical assessment to inform immediate management. Several studies support this application of the test battery.[59,60] In a study conducted by McCrea et al, patients who experienced mTBI underwent computerized neurocognitive testing on a regular basis, starting in the acute phase after their injuries. The study data indicate that dramatic improvement in test scores occurs by 72 hours post-injury and that by day 7 post-injury most individuals have recovered to baseline.[25] This is further supported by Kelly et al, who note that most symptoms and deficits tend to resolve by day 10 post-injury, and if not, more in-depth analysis (beyond computerized neurocognitive testing) is required.[60, 6] The second approach is to administer the ANAM4 after a patient is symptom-free and is characterized by USNA's use of ANAM4, which is intended to identify signs of mTBI that are slow to resolve or that may not be obvious through other means of post-injury assessment. The ongoing comparison to a midshipman's individual baseline, after symptom resolution, reduces the risk of false-positive or false-negative diagnoses and prevents the midshipman from returning to full activities prematurely. This approach is supported by a study conducted by Fazio et al that used ImPACT to assess concussed and non-concussed athletes one week after sustaining an mTBI. All of the injured athletes demonstrated significantly lower test scores than the uninjured controls. Further, injured athletes who reported full resolution of symptoms after one week still scored significantly lower than their uninjured counterparts, indicating that full resolution of physical

symptoms may not indicate complete recovery.[61] A study conducted by Haran et al in 2013 also supports the use of ANAM4 beginning after the acute injury phase following mTBI has passed. The study investigated the return to neurocognitive baseline in Marines using ANAM4 tests administered between 2 and 8 weeks post-deployment and between 3 to 12 months post-deployment, and found that cognitive deficits can persist for 1 to 3 months after the initial injury.[6,62]

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3. Sensitivity, Specificity, and Reliability of Computerized Neurocognitive Testing

Current DoD policy mandates that each Service member complete Automated Neurocognitive Assessment Metrics 4 (ANAM4) baseline testing within 12 months prior to deployment. However, recent budget constraints in combination with new research suggesting that normative data may be sufficient to identify decreases in neurocognitive function post-mild traumatic brain injury (mTBI) has prompted a review of the policy and its associated costs.

Comparing the relative effectiveness of individual baseline ANAM4 results and normative data in post-injury assessments is complex. Most experts agree that, logically, a valid high-quality individual baseline would provide the most accurate data for clinicians to make a well-informed return-to-duty decision for a given individual. However, recent research indicates that collecting an accurate baseline is challenging and that many of the available baselines in the military's ANAM4 data repository may not be of sufficient quality.[11,15,16] Other elements that must be considered in this comparison are the value that baseline testing provides for individuals who ordinarily perform significantly above or below the norm; challenges in appropriately interpreting ANAM4 test results; and the size and stratification of the existing military ANAM4 normative database.

Several quantitative and qualitative measures are used in evaluating the accuracy and effectiveness of using individual baselines versus normative data for post-injury comparison. These measures include sensitivity, specificity, and test/re-test reliability. It is desirable that a neurocognitive test demonstrate high sensitivity and specificity. As defined by McCrea et al,

> [sensitivity]…refers to the probability that an injured participant will be identified as "abnormal" by a change in test performance. At time points subsequent to time of injury, sensitivity values indicate the probability that a player originally injured continued to be classified as "abnormal" according to at least one of the test measures. Specificity… refers to the probability that a control participant will be correctly classified as "normal" using the same method.[25]

Test/re-test reliability is an indicator of an NCAT's consistency. Cole et al define test/re-test reliability as "the association between the scores obtained by a single examinee taking the same test on two or more different occasions."[6] Reliability is usually expressed using Pearson's *r* coefficient or intraclass correlation values. The higher the *r* value or intraclass correlation, the higher the NCAT's reliability. Reliable change indices may also be used to describe the reliability of an NCAT. High test/re-test reliability indicates a robust testing platform that minimizes or accounts for the impacts of practice effect, testing environment, psychological state, and attitude on individual test scores.[6]

3.1 Test/Re-Test Reliability

A key argument against the continued use of computerized baseline testing is that the reliability of available test batteries is not high enough to ensure that baselines are valid.[6,38] Environmental factors, natural variation in cognitive function, and inconsistent data interpretation methods may

preclude accurate baseline comparisons.[52] When compared with other NCATs such as ImPACT, CogState Sport, and CNS Vital Signs, ANAM4 demonstrates similar reliability and validity.[23] Cole et al conducted a study in healthy, active duty Service members, in which study participants were assigned to take one of the four NCATs listed above twice within a 30-day period. They found that, within their healthy study population, most NCATs showed low intraclass correlation in both individual subtests and as a whole. Overall, they concluded that test-retest reliabilities were consistent with those previously reported in the literature and "less than suggested for clinical use."[6] One methodologic concern with the study is that non-standardized computers were used for testing, potentially leading to significant error in reaction time-dependent subtests.[6]

Another factor that affects test results is mindset. Some research suggests that when individuals take neurocognitive test batteries while anxious they demonstrate lower test scores. A 2003 study by Suhr et al[63] explored a theory called "diagnosis threat," which is thought to lower neurocognitive test scores due to anxiety, depression, and increased effort associated with fear of a poor diagnosis. The study observed test performance in individuals with a history of mTBI. The experimental group was informed that they were being tested because of their head injury. They were matched with controls who had a similar mTBI history, but were not informed that the testing was related to their injuries. Suhr et al found that the experimental group performed worse than the control group on tests of delayed recall, psychomotor speed, working memory, and attention. After assessing both groups for depression and for effort, researchers found that depression did not account for the difference between groups and that both the control group and the experimental group exhibited the same level of effort. They concluded that even the threat of being perceived to have cognitive deficits because of mTBI could worsen performance on neurocognitive assessments.[63]

3.2 Impact of Self-reported mTBI on Post-Deployment Neurocognitive Test Scores

Some studies have investigated the effect of self-report of TBI during deployment on post-deployment neurocognitive test scores. A 2014 study by Cooper et al examined the factors associated with neurocognitive performance in Service members who self-reported having experienced mTBI while deployed overseas during Operation IRAQI FREEDOM (OIF) or Operation ENDURING FREEDOM (OEF). Service members who enrolled in the study had redeployed and reported persistent cognitive difficulties and mTBI-related symptoms. These individuals took the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test to measure their cognitive function. The researchers found that overall the Service members scored in the lower end of the average range. In analyzing which factors had the greatest impact on the test score, they found that test taker effort had the greatest effect on score, followed by symptom severity. They found that a significant number of study participants failed the RBANS effort index, highlighting the importance of including a robust effort measure when administering neurocognitive assessments. When analyzing the scores of all Service members, including those who failed the effort index, self-reported symptoms accounted for a statistically significant effect on test scores. However, when analyzing only the test scores of Service members who demonstrated sufficient effort on the RBANS, it was determined that factors such as demographics, nature of the injury, and reported symptom severity had a relatively small though statistically significant impact on test scores.[64] It is important to note that

the study only included individuals who were not in the acute phase of mTBI, which may explain why reported symptoms were not associated with a statistically significant decrease in test scores.

A 2009 study by Ivins et al further supports this theory. The study examined a sample of U.S. Army soldiers who had served in Iraq and/or Afghanistan to determine whether a self-reported history of deployment-related TBI, lifetime history of TBI, and current post-concussive symptom status affected cognitive test performance.[65] The results did not demonstrate either an "association between having a history of mTBI and poor ANAM performance" or an "association between poor ANAM performance and the reported number of TBIs, injury severity, and the number of problematic post-concussive symptoms." Bruce and Echmendia also found that there was no correlation between poor scores and self-reported total number of lifetime TBIs, injury severity, or ongoing symptoms.[66]

3.3 Sensitivity and Specificity

The symptoms of mTBI are variable and poorly defined.[27] Individuals who have experienced mTBI manifest symptoms differently depending on the part of the brain that was injured, making the impact of mTBI on various neurocognitive functions difficult to assess. Normal fluctuations in neurocognitive function that occur because of shifts in environment, mood, and practice can distort or obscure changes in cognitive function that occur with mTBI. These challenges can decrease the sensitivity and specificity of ANAM4. Although ANAM4 is used in conjunction with other clinical information when assessing mTBI, researchers have investigated its effectiveness independently to study how sensitivity and specificity change when post-injury test results are compared with baselines versus normative data. A 2013 study conducted by Mihalik et al compared serial tests of healthy athletes and concussed athletes to measure the sensitivity and specificity of ANAM4's test battery. Using the baselines of the healthy athletes as a norm, they found that ANAM4 did successfully identify cognitive deficits in a small number of athletes who experienced mTBI.[38] However, they found that sensitivity was low for both the individual subtests and the test battery as a whole. Sensitivity increased to 50 percent when a patient's symptom score was included in analysis of the test results, but not significantly enough to allow ANAM4 to serve as an independent mTBI assessment method. Mihalik et al found that for individual subtests, as well as the combined battery, specificity was high (greater than .80). This indicates that while ANAM4 did not demonstrate high sensitivity, it accurately identified deficits in cognitive function in concussed athletes.[38] These findings are supported by the research of Broglio et al, who studied the sensitivity of NCATs in detecting cognitive deficits after mTBI. The study found that most NCATs identify declines in cognitive function in at least one area for most concussed individuals.[15] However, this level of sensitivity was only achieved when test results were interpreted in conjunction with symptom severity.

A 2012 study by Bryan et al that investigated the neurocognitive performance of Service members who experienced mTBI while deployed found that mTBI does affect neurocognitive performance.[67] Unlike the previous studies, this study examined the ANAM4 tests scores from neurocognitive assessments completed in theater as part of the initial injury assessment, which included a full physical and psychological evaluation. The results indicated that service members with mTBI showed greater declines in some speed and throughput subtests compared

to service members without TBI. No significant differences in accuracy were noted. The authors concluded that the findings “support the use of the ANAM as a clinical screening tool among at-risk populations, such as those with a positive history of TBI,” and that focusing on reaction times “may serve as a more sensitive measure of cognitive decline.”

A 2001 study conducted by Echemendia et al investigated the ability of several neuropsychological test batteries to detect declines in cognitive function following mTBI. The study model, conducted in college-level athletes, collected baseline data for all athletes. Each athlete was paired with a control, and both received a follow-up neurocognitive assessment following mTBI that occurred during game play. Students who sustained mTBI were tested 2-hours, 48-hours, 1-week, and 1-month post-injury for cognitive impairment. Data indicated that injured athletes showed cognitive impairment for the 2-hour, 48-hour, and 1-week assessments. At the 1-month mark, the control group and the injured group were indistinguishable, and both were performing at levels higher than their baseline, suggesting that there may be a practice effect. The authors concluded that baselines may be useful; however, neurocognitive assessments are highly variable and should only be considered as part of a comprehensive evaluation.[41] This study also indicates that computerized neurocognitive tests demonstrate sufficient sensitivity and specificity in detecting neurocognitive impairments after mTBI when acute phase post-injury tests are compared to a baseline.

Relatively few studies examine how sensitivity and specificity shift depending on whether individual baselines or normative data are used for comparison in a post-mTBI assessment. A study conducted by Schmidt et al in 2010 compared the sensitivity and specificity of ANAM4 using gender norms and baseline values for comparison. One thousand sixty college athletes underwent ANAM4 testing that included initial and end-of-test simple reaction time assessments to assess fatigue after mental exertion. Six hundred thirty-eight healthy athletes served as matched controls for the 258 individuals who experienced mTBI, and 175 of the injured individuals had pre-injury baselines for comparison. After analyzing each subtest and the battery as a whole using both baselines and gender-specific normative data, they found that the baseline comparison method identified 2.6 times as many impairments as the normative method in the initial simple reaction time test. Normative data identified 7.6 times as many impairments in mathematical processing. For all other measures, the baseline comparison and normative data were in statistical agreement. The authors state that while these differences are significant, the overall sensitivity of each subtest to mTBI must be taken into account. Certain subtests, notably simple reaction time, appear to demonstrate higher sensitivity to mTBI than others.[11,68] The authors note that the overall number of impairments for the first simple reaction time test was so low that, when the test is administered on a large scale, the relative improvement seen in detecting declines in the first simple reaction time test using baseline as opposed to normative comparisons was minor.[7]

Echemendia conducted another study comparing the effectiveness of the normative method versus the baseline method for assessing mTBI using ImPACT. Using a population of 223 college athletes with ImPACT baselines, they compared two approaches for calculating reliable change for the baseline method, finding that the Gulliksen-Lord-Novick (GLN) method consistently identified more injured subjects than the Jacobson and Truax approach. They then compared the number of athletes identified as cognitively impaired as a result of their injuries using the GLN method versus the normative method. They found significant agreement between

the methods, noting that the majority of injured athletes were correctly identified using normative data alone. The authors concluded that "the majority of collegiate athletes who experience clinically meaningful post-concussion cognitive decline can be identified without baseline data."[69]

In contrast to the findings of Schmidt et al, Echemendia, and Register-Mihalik, a 2014 study by Louey et al found that the baseline method for assessing mTBI is more sensitive than the normative data method. Using norms stratified by age and education, they found that both methods were highly specific and, overall, both methods correctly classified subjects as healthy or injured. However, when the injured athletes identified by the baseline method were compared to the number identified by the normative method, they found that 27.6 percent of the injured athletes who had been identified using the baselines method were not identified using normative data.[43]

The findings of Louey et al are supported by a 2015 study conducted by Hinton-Bayre.[70] In this study, Hinton-Bayre reviewed the studies published by Echemendia, Schmidt, and Louey, noting that the study designs and analyses employed in the Schmidt and Echemendia studies were flawed and resulted in inaccurately high estimates of the sensitivity and specificity of normative data. Hinton-Bayre also expressed concern regarding the use of computerized neurocognitive testing, preferring the use of traditional pencil and paper assessments to compare the baseline versus normative data approaches to evaluating mTBI. In a study of professional rugby players, Hinton-Bayre found that if individual baselines are not available, normative data, stratified by age, ethnicity, IQ and previous mTBIs, does contribute beneficially to the management of mTBI. However, individual baselines were much more informative, accounting for intra-individual variation and reducing the occurrence of false positive and false negative classifications.[70] As with the Louey study, it should be noted that the sample size for this study was small, comparing only 27 injured players with 26 uninjured controls.

There are many challenges associated with assessing the impact of test-retest variability in accurately interpreting results obtained from computerized NCATs.[16,38,71] This inherent variability complicates analysis of post-mTBI test results, especially in cases when a Service member's healthy baseline ANAM4 test score is significantly above or below the average.[71] The Service members who fall within the tails of the distribution face a greater risk of misdiagnosis and incorrect return-to-duty decisions, because normative data would not provide a valid comparison to determine when these individuals returned to the normal range of function.

Multiple subject matter experts indicated that these cases (in the tails of the distribution) pose a significant challenge, especially when an individual's baseline is not available. Service members who test significantly above or below average when healthy run a significantly higher risk of misdiagnosis when normative data are used in analysis of ANAM4 results. If Service members who test above average experience an mTBI with the associated symptomatology and decline in cognitive function, comparison of their post-injury ANAM4 scores with normative data may not indicate that their cognition is compromised, as their ANAM4 score may have decreased from above average to the norm.[71] The resulting false-negative diagnosis may result in the Service member being returned to duty prematurely, potentially placing them and their mission at risk, while also leaving a persistent decrement in cognitive function unrecognized.

Conversely, Service members who would test below average on the ANAM4 when healthy run the risk of false-positive diagnoses when their post-mTBI ANAM4 scores are compared to normative data. Without a previous healthy baseline, these individuals will demonstrate below average cognitive function consistent with mTBI; however, as their symptoms resolve over time, even if their ANAM4 scores improve to what would be their normal baseline function, it will appear as if they have a persistent deficit in cognitive function relative to the norm. A 2013 study by Roebuck-Spencer et al highlights this phenomenon and endorses the value of baseline testing. It compared the rates of atypical (potentially impaired) performance on ANAM4 when soldiers' post-deployment test scores were compared with normative data and their individual baselines. They found that both methods identified atypical results at a similar rate. However, "a high percentage of individuals classified as atypical" using normative data "showed no change from baseline, indicating that using norms alone may result in a large number of false positive errors." The resulting misclassification can result in increased costs and use of medical resources.

Finding 1.1: Current evidence is inconclusive on whether using individual baseline computerized neurocognitive assessment test results is more advantageous, on a population level, than using an optimally stratified normative dataset in evaluating and managing mild traumatic brain injury, including assessing return to duty decision making and prognosis.

Finding 1.2: The current ANAM4 military normative dataset is stratified solely by age and sex and does not accurately estimate baseline neurocognitive function in individuals who score at the high or low ends of the scale. Efforts are currently underway to expand and further stratify this dataset to improve accuracy in estimating cognitive deficits related to mild traumatic brain injury.

Recommendation 1: DoD should continue to analyze existing ANAM4 data to determine whether an optimally stratified normative dataset can be developed that is capable of accurately estimating baseline neurocognitive function, including for individuals who score at the high or low ends of the scale. Specific stratification variables to consider adding include education, rank, standardized test scores, race/ethnicity, and environmental factors such as socioeconomic status.

Finding 2: It is not apparent that an adequate overall assessment of the utility of the current ANAM4 testing program in evaluating and managing mild traumatic brain injury has been accomplished. Moreover, it is not apparent that clinical evaluation and disposition data have been centrally compiled to accomplish this analysis.

Recommendation 2: DoD should analyze current clinical data from mild traumatic brain injury evaluations to determine in what proportion of cases ANAM4 testing provided information of clinical value that was a contributing factor in overall management and disposition of the patient. As part of this analysis, the value of having an individual baseline for comparison should be assessed.

Finding 3: Current evidence is inconclusive regarding the value of routine pre-deployment baseline ANAM4 testing.

Recommendation 3: DoD should request that legislation requiring routine pre-deployment neurological cognitive assessments be rescinded to allow discontinuation of routine pre-deployment ANAM4 baseline testing. DoD should instead conduct prospective research using neurocognitive or other assessment tools to evaluate their usefulness in the management of mild traumatic brain injury and return-to-duty decision-making.

3.4 Effect of ANAM4/NCATs on Clinical Decision Making

There is little research on the impact of ANAM4 on clinical decision making and patient outcomes. A study conducted by Kelly et al in 2012 investigated the impact of ANAM4 use on the ability of clinicians to correctly identify cognitive deficits. The researchers compared the sensitivity and specificity with which clinicians were able to identify decreases in procedural reaction time (PRT) and simple reaction time (SRT) performance when using ANAM or traditional methods when assessing patients who experienced loss of consciousness or post-traumatic amnesia due to mTBI. They found that using ANAM4 increased the discriminant ability of clinicians to detect changes in SRT and PRT. Using ANAM4 did not increase specificity, but it did increase the sensitivity, allowing clinicians to more easily identify patients experiencing cognitive deficits.[11] Further research is needed into how clinicians use ANAM4 and how much it affects their decisions in managing mTBI; however, this study demonstrates that computerized neurocognitive testing does provide beneficial information in the overall assessment of mTBI.

A study conducted by Van Kampen et al in 2006 investigated the role of neurocognitive testing in athletes following sports-related mTBI. The researchers used ImPACT to collect pre-season baselines and post-injury and post-season test scores for high school and college athletes. Study participants were asked to report their symptoms in addition to completing ImPACT testing. The study found that athletes were less likely to be correctly identified as having an mTBI when diagnoses relied solely on reported symptoms, but when post-injury ImPACT scores were analyzed, a greater number of injured athletes were correctly identified. The authors note that this is indicative of "an imperfect agreement between self-reported symptoms and decreased neurocognitive test scores after concussion."[72] Van Kampen's work is supported by Fazio et al, who also found that reliance on self-reported symptoms alone is not as accurate as administering neuropsychological testing in addition to a symptom report.[61]

Assessing prognosis and predicting return-to-duty/play time after an mTBI can be difficult. Research indicates that there are several predictors for prolonged recovery including symptoms of headache lasting longer than 3 hours, difficulty concentrating, retrograde amnesia, or loss of consciousness.[18] No studies on the usefulness of ANAM4 in predicting long-term prognosis were located, however, some studies examined ANAM4 scores and return-to-duty time. A study by Norris et al in 2013 found a correlation between ANAM4 simple reaction time scores and length of recovery following an mTBI. In their retrospective analysis of medical records of Service members who experienced mTBI, they found that the individuals who scored in the lowest 25 percent on the ANAM4 reaction time-based subtests had a median return-to-duty time

of 19 days, whereas those in the upper 25 percent had a median return-to-duty time of approximately 7 days.[17]

Finding 4: ANAM4 testing has not yet been shown to consistently or significantly contribute to assessing long-term prognosis after a mild traumatic brain injury.

Recommendation 4: DoD should analyze post-injury test scores and long-term data documenting the recovery of Service members after a mild traumatic brain injury to determine if post-injury ANAM4 scores consistently or significantly contribute to the assessment of prognosis.

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4. AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS 4 NORMATIVE DATABASE AND DATA REPOSITORY

Since the Neurocognitive Assessment Tool (NCAT) program was initiated in 2008, the U.S. military has collected more than 1.8 million baseline Automated Neuropsychological Assessment Metrics 4 (ANAM4) test results, which are stored in a data repository. An initial normative database specific to the U.S. military population was created in 2008 with 107,000 of these test results for use in evaluating mild traumatic brain injury (mTBI). This database is currently stratified by age and sex only.[5] Experts in the field of neuropsychological testing suggest that further stratifying the military normative database may improve statistical accuracy in identifying changes in cognitive function when evaluating mTBI with post-injury ANAM4 test scores. Research showing that demographic factors such as education, handedness, ethnicity, and rank may affect performance on neurocognitive testing[19,20] supports the need for a more highly stratified database. Other variables suggested by subject matter experts that may be of value include occupation and standardized testing scores (such as Armed Services Vocational Aptitude Battery). Addition of these strata may require the incorporation of additional baselines for underrepresented subgroups within the current military population.

4.1 THE CURRENT DATA REPOSITORY

The ANAM program is currently managed by the U.S. Army Medical Department (AMEDD). Until recently, ANAM test results were stored in a data repository that was not structured in a format conducive to statistical analysis. Clinicians could access a Service member's previous test results by submitting a request to a 24/7 ANAM call center via telephone, email, or fax, but it was not possible to easily access large numbers of scores to conduct larger-scale research. As such, it was a significant untapped resource for research on mTBI, retrospective analyses, and development of an improved normative database. In efforts to utilize this vast quantity of data, the ANAM program office has undertaken the conversion of the data repository into a true database. As of August 2015, the DoD ANAM program office had successfully converted more than 1.8 million ANAM4 records into a database format, identified 1.1 million records suitable for use in constructing an improved normative dataset, and had begun analysis to identify sources of additional demographic factors that may be applied to further improve the stratification and accuracy of the normative dataset.[5]

4.2 MAINTAINING THE NORMATIVE DATABASE

The current U.S. military ANAM4 normative database was created in 2008. Since a normative database should reflect the population being tested[73] and the demographic characteristics of the military population will likely change over time, it should be updated on a regular basis. Thus, there must be an ongoing effort to continually collect and update the baselines to reflect the current demographic distribution of the military population to maintain a current normative database. Since the current ANAM program targets military members who are scheduled to deploy for baseline testing, it is possible that the database over represents young, healthy, enlisted males.

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5. Automated Neuropsychological Assessment Metrics Program Costs

5.1 Current Program Costs

In 2008, Congress included a provision in the National Defense Authorization Act requiring all deploying Service members to undergo pre-deployment baseline neurocognitive testing.[23] As an initial response to this requirement, DoD elected to use the Automated Neuropsychological Assessment Metrics (ANAM) software to conduct the required baseline testing and continues to use ANAM4.[4] DoD had sold the ANAM software license to Oklahoma State University and, until 2014, was paying an annual licensing fee for up to 400,000 ANAM4 traumatic brain injury (TBI) assessment battery tests.[5] DoD also contracted with the Eyak Corporation to provide trained contract staff to administer the ANAM4 tests as needed. Prior to its adoption as the NCAT to conduct pre-deployment baselines in 2008, the ANAM was used primarily for research on the effects of medication and other chemicals on neurocognitive function.[10] Work on developing a neurocognitive ANAM assessment for mTBI began in 2001, but use of the mTBI battery was not widespread.[10,50] However, as a result of the new requirement for baseline testing on all deploying Service members and the associated licensing and contracting expenses, the overall cost of the ANAM program increased significantly. The overall cost continued to increase through 2011 and then gradually decreased starting in 2012 as the total number of deployments decreased.[21] As summarized in Table 2, DoD spent approximately $47,723,144 to conduct ANAM4 testing between Fiscal Year (FY) 2009 and the 2nd quarter of FY 2015.

Table 2. Total Number of ANAM4 Tests and Associated Costs, FY 2009 - 2nd Quarter of FY 2015[5]

FY	Number of Tests Administered*	Licensing Fee	Contract Costs
FY 2009	296,272	$2,000,000	$11,506,169.01 **(FY 2009-2010)**
FY 2010	307,616	$2,000,000	
FY 2011	325,037	$2,000,000	$7,192,749.27
FY 2012	255,134	$2,000,000	$4,897,378.00
FY 2013	246,619	$2,000,000	$4,622,299.70
FY 2014	196,368	$2,000,000	$4,410,268.31
FY 2015 (Quarters 1+2)	78,023	$1,000,000 for Q1+Q2	$2,094,279.67 for Q1+Q2**
Totals:	**1,705,069**	**$13,000,000**	**$34,723,146.96**
		Total Cost (Licensing fees + contract costs):	**$47,723,143.96**

* Total number of tests includes reported baselines, post-injury, clinical, post-deployment, and unspecified tests.
**Contract cost listed is one half of the annual contract cost for FY 2015.
Adapted from ANAM Program Office, 2015.

The current licensing and contracting model for the ANAM4 program remains similar to the 2008 model. DoD pays a licensing fee to Oklahoma State University; however, instead of

paying $2 million a year for up to 400,000 test administrations, DoD now pays $1 million for up to 100,000 tests per year, with the option of administering more tests for a fee of $140,000 per 20,000 additional tests. DoD continues to contract with Eyak Corporation to administer on-site ANAM4 testing. When the total cost of the program and the total number of tests administered between FY 2009 and FY 2014 are taken into account, the estimated average cost of each test is $26.81.

Table 3. Total Number of Tests and Costs per Year[5]

Fiscal Year	Total Tests Administered	Contract Cost	License Fee	Average Cost Per Test Per Year***
FY 2009	296,272	$11,506,169.01*	$2,000,000	$26.58
FY 2010	307,616		$2,000,000	
FY 2011	325,037	$7,192,749.27	$2,000,000	
FY 2012	255,134	$4,897,378.00	$2,000,000	$27.03
FY 2013	246,619	$4,622,299.70	$2,000,000	$26.85
FY 2014	196,368	$4,410,268.31	$1,000,000	$27.55
FY 2015 (Quarters 1+2)	78,023	$2,094,279.67**	$1,000,000	$39.66

* Hardware purchases accounted for a larger proportion of contract costs in FYs 2009-2011.
**Contract cost listed is one half the annual contract cost for FY 2015.
***These costs should be considered approximate estimates based on the information provided.
Adapted from ANAM Program Office, 2015.

According to data obtained from the ANAM program office, a total of 1,841,489 tests have been administered as of the second quarter of FY 2015 (Table 4). Of that number, 1,627,202 were pre-deployment baselines and 84,524 tests were administered for post-deployment, clinical, injury, or recovery TBI assessments. An additional 30,751 tests were administered for unspecified reasons.

Table 4. Breakdown of Total Number of ANAM4 Tests by Reason[5]

Service	Pre-Deployment	Post-Deployment	Clinical	Injury	Recovery	Unspecified	Total
Army	1,049,441	52,174	11,490	2,301	241	20,723	1,136,370
Air Force	303,738	1,646	1,415	207	17	4,564	311,587
Marine Corps	247,050	824	9,921	2,054	331	2,587	262,767
Navy	80,229	522	834	135	22	911	82,653
Coast Guard	2,195	1	4	0	0	7	2,207
Non-Military	43,549	240	120	24	1	1,959	45,893
TOTAL	1,726,202	55,407	23,784	4,721	612	30,751	**1,841,477**

Adapted from ANAM Program Office, 2015.

As shown in Table 5, baselines comprise 93.7 percent of total tests administered. Post-deployment, clinical, injury and recovery assessments comprise 4.6 percent of the total, and tests conducted for unspecified reasons comprise 1.7 percent. The relatively low number of tests administered for post-deployment, clinical, injury, and recovery assessments in the management of mTBI compared to the reported incidence of mTBI may be related to a number of factors. Military clinicians do not always use ANAM4 in their assessment and management of mild traumatic brain injury (mTBI) since the ANAM testing policy applies only to mTBIs that occur during deployment,[4] and approximately 80 percent of TBIs occur in garrison.[74] Clinicians who specialize in caring for mTBI patients in the non-deployed setting may have access to a more sophisticated set of neuropsychological and physical assessments that may not be available in deployed settings.[27] Another factor may be that earlier in the program, baseline ANAM4 scores were not perceived to be readily accessible, making it difficult to compare post-injury test results to a Service member's baseline. Finally, even in the deployed environment, the severity of the TBI may affect the use of ANAM4 in assessing the injury. In cases of very mild TBI that occur in theater, clinicians may not refer Service members for further testing with ANAM4 if they do not report any symptoms and they do not demonstrate any impairment on the Military Acute Concussion Evaluation (MACE), an initial screening conducted after a concussive event (or high-risk exposure) to assess whether a Service member has sustained an mTBI.[75] A full breakdown of the ANAM4 test reasons by date of test administration can be found in Appendix D.

Table 5. Breakdown of Test Reason by Percentage of Total Number of Tests Administered[5]

Service	Pre-Deployment	Post-Deployment	Clinical	Injury	Recovery	Unspecified	Total
Army	92.3%	4.6%	1.0%	0.2%	0.0%	1.8%	100%
Air Force	97.5%	0.5%	0.5%	0.1%	0.0%	1.5%	100%
Marine Corps	94.0%	0.3%	3.8%	0.8%	0.1%	1.0%	100%
Navy	97.1%	0.6%	1.0%	0.2%	0.0%	1.1%	100%
Coast Guard	99.5%	0.0%	0.2%	0.0%	0.0%	0.3%	100%
Non-Military	94.9%	0.5%	0.3%	0.1%	0.0%	4.3%	100%
TOTAL	93.7%	3.0%	1.3%	0.3%	0.0%	1.7%	100%

Adapted from ANAM Program Office, 2015.

5.2 Cost Associated with Maintenance of a Normative Database

One of the primary questions asked of the Defense Health Board was whether a normative database could be used in lieu of continuing baseline testing. A preliminary analysis of the current ANAM4 normative database, stratified only by sex and age (in one year increments), showed a significant error rate in classifying scores which were greater than one standard deviation above or below the mean. For asymptomatic individuals with no self-reported history of TBI in this group, analysis using the normative dataset yielded a false positive rate of 18.0 percent, a false negative rate of 46.3 percent, and an overall error rate of 64.3 percent.[5] Development of an improved ANAM4 normative database is currently in progress.

Presuming that use of an optimally stratified normative database could provide performance metrics similar to those found using baseline comparison testing, routine baseline testing might be discontinued. However, the normative database would still need to be updated periodically with additional baseline tests as the demographic profile of the military changes over time. Additional research is needed to determine how many and how frequently additional baselines would need to be obtained to keep the normative database current. DoD would also need to retain the infrastructure necessary to conduct post-injury and post-deployment ANAM4 testing to assess the cognitive function of Service members who sustain mTBI during deployment. Since this post-injury/post-deployment testing infrastructure would need to remain in place, it remains unknown whether there would be a significant cost savings on licensing or contracting fees compared to the current model.

As discussed in Section 3, using normative data in lieu of individual baselines in the assessment of mTBI may increase the possibility of false negative and false positive classifications. Service members whose cognitive function normally falls significantly below or above the average are especially at risk for post-mTBI misclassification, as lower functioning individuals are more likely to register as false positives and higher functioning individuals are more likely to appear as false negatives. These false indications could potentially have significant impact; Service members who test below the norm, even though that reflects their true baseline, may be subjected to unnecessary and expensive testing, may be inappropriately prevented from returning to duty, and may be incorrectly deemed to have a Service-connected disability. High functioning Service members who fall within the normal range on post mTBI testing, even though they have a persistent mTBI-related cognitive deficit, may not receive appropriate management, may be returned to duty prematurely, and if the deficit is permanent, may not be recognized as having a Service-connected disability.

5.3 Expanding Testing Beyond the Deployment Cycle

The larger population in garrison, combined with injuries from training, motor vehicle accidents, sports, and other recreational activities results in a larger number of mTBIs. Nearly 80 percent of all TBIs occur in garrison, and mTBIs comprise approximately 80 percent of the total number of TBIs that occur in Service members. Clinicians are not currently required to administer the ANAM4 as part of an assessment of TBI that occurs in garrison, but the testing is available in many locations, and the test battery has been approved as an optional evaluation in a new garrison TBI management policy.[76] If research indicates that ANAM4 is a valuable component of the assessment and management of mTBI, expanding ANAM4 testing beyond the deployment cycle may be beneficial. There are many factors that may affect the overall cost of expanding the program to non-deploying personnel, such as the size of the population that should undergo baseline testing. For example, baselines could be conducted on all personnel, only on those who have occupations or participate in activities considered high risk for mTBI, or routine baseline testing could be discontinued. If the approach of conducting baselines on all Service members or a high-risk subset were adopted, the resulting increase in testing would likely increase the software-licensing fee and possibly the contract expenses for test administration. Even if expanded baseline testing was not planned, some level of additional baseline testing may be needed to ensure the normative database is regularly updated and reflects the demographic

characteristics of the garrison population, which are likely different from those of the deployed population.

> **Finding 5:** Currently, there is insufficient evidence to support expanding the use of ANAM4 administration, to include periodic baseline assessments of cognitive function, outside of the deployment cycle.
>
> **Recommendation 5:** DoD should defer a decision to expand ANAM4 baseline testing outside of the deployment cycle until additional research demonstrates that baseline testing improves the evaluation and management of mild traumatic brain injury.

5.4 Options to Reduce Costs

Recent cost savings in the ANAM testing program have occurred primarily due to restructuring of the software-licensing fee and decreased demand for testing with fewer deploying personnel. Assuming there is no change in the current neurocognitive testing policy, annual costs would likely remain stable unless there was a significant increase in the number of personnel deploying.

One approach to reduce or limit costs would be to limit individual baseline testing to sub-populations that are at higher risk of TBI while deployed due to their military occupational specialty or deployment duties. However, personnel who do not receive baseline testing may perceive they are not being provided an appropriate opportunity to accurately document their baseline cognitive function in the event they experience an mTBI. Considering the cost necessary to maintain a minimum ANAM4 testing infrastructure, it is not clear how significant the cost savings may be with this approach.

Overall, questions remain regarding the utility and cost-effectiveness of ANAM4 testing in managing mTBI. Whether using an optimally stratified normative database would be as accurate as using individual baseline test results to identify cognitive deficits following mTBI at a lower cost remains unclear.

5.5 Costs Associated with the Immediate Post-Concussion Assessment and Cognitive Testing Program

The Immediate Post-Concussion Assessment and Cognitive Testing Program ImPACT is an Internet-based test currently used by the U.S. Army Special Operations Command (USASOC) to assess for cognitive deficits associated with mTBI in Service members.[77] The contract for FY 2015 has associated costs of $2 per baseline test and $8 per post-injury test. There is an additional option to train four medical officers for $3,840 to administer and interpret the ImPACT test. The contract requires that the test provider provide 24/7 access to the online ImPACT test and test results, including all previous tests taken by any Service member. The test providers also deliver technical support as needed.[22] The program does not provide for equipment or proctors to conduct testing.

Finding 6: DoD is currently using at least two NCATs (ANAM and ImPACT) to assess neurocognitive function. There are significant differences in the pricing structure for these tools and studies have not shown either tool to have a distinct overall advantage in contributing to the management of mild traumatic brain injury.

Recommendation 6: DoD should conduct a competitive bidding process to select the most cost-effective approach to meet requirements for all non-specialized neurocognitive assessments for the management of mild traumatic brain injury.

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6. Areas for Future Research

Recent publications outline the need for additional research on the development and appropriate use of computerized neurocognitive assessment tools (NCATs).[13,16,24,25] These tools have become widely used in the assessment and management of mild traumatic brain injury (mTBI); however, challenges remain in improving their sensitivity, accuracy, and the methodology for interpreting test results. Based on a review of the current ANAM4 program and available literature and expert opinion, the Subcommittee has identified several focus areas for future research, as outlined below.

6.1 ANAM4 Program Cost-Effectiveness

There is no apparent consensus on the best approach to measure cost-effectiveness of computerized NCATs and no published research was located assessing the cost-effectiveness of the ANAM4 program. As discussed in Section 5, DoD was recently able to reduce the cost of the overall program due to the decreased demand for testing with fewer personnel deploying. The effectiveness of the ANAM4 in contributing to the management of mTBI, including decisions on return to duty, has not been adequately assessed. Some clinicians who are using or had used the ANAM4 endorsed the value of the test in providing useful objective data to assess cognitive function following an mTBI or high-risk exposure. They indicated the information was useful in making decisions on returning Service members to duty or referring them for additional evaluation. Additional work on defining and capturing the information necessary to determine overall cost effectiveness is needed. The 1.8 million ANAM4 baselines collected by DoD will provide valuable data for this work.

6.2 Accuracy of Using Baseline versus Normative Values in Assessing mTBI

As discussed in Section 3, there is general consensus that comparing post-mTBI NCAT scores to valid pre-injury baselines is, in theory, more accurate than comparing post-injury scores to normative values.[16] However, on a population level, studies have not clearly or consistently demonstrated this advantage.[7,36,38] The inherent variation in the quality of baselines collected via large-scale computerized testing under varying conditions, the inherent temporal variation in individual human cognitive function with physical or psychological stressors, the inherent limitations in the current generation of NCATs, and limitations in the methods for analyzing test results all likely contribute to this phenomenon. DoD is currently developing a larger and more stratified ANAM4 normative database. Upon completion, a retrospective comparison of baseline and normative data with ANAM4 data from post mTBI clinical evaluations should provide important information on the relative value of having baseline test data. As stated by Iverson et al, this research will help determine whether having individual baselines contributes in a meaningful way to the evaluation and management of mTBI and return-to-duty decisions in the context of a multidimensional clinical assessment.[16]

6.3 Other Neurocognitive Assessment Tools

The field of computerized neurocognitive testing is growing, with new tests and technologies emerging regularly.[24,78] As technology continues to evolve, accessibility, feasibility, and accuracy are important factors to consider as the Department of Defense (DoD) reviews new assessment tools to evaluate and manage mTBI. Additional research into the psychometric properties of existing NCATs in the assessment of mTBI is needed, particularly with respect to blast-related TBI.[79,80] These studies will provide data that will help DoD determine whether ANAM4 has comparable or superior reliability and clinical utility compared to other NCAT batteries.

DoD briefly funded development and testing of a new neurocognitive assessment tool, the Defense Automated Neurobehavioral Assessment (DANA), as a hand-held device to assess mTBI in military populations. Unlike ANAM4, DANA may be administered on a smartphone, making the test more easily accessible to evaluate injured Service members in the field.[81] DANA was cleared by the FDA as a medical device in October 2014,[82] however, at the time of this report, DoD is no longer funding additional development of this device.

It is important to remember that NCATs are only one component of a comprehensive clinical evaluation of mTBI. In light of this, DoD is pursuing research on new assessments such as brain imaging, postural stability, vision testing, biomarkers, and other physiological evaluations. The 2009 clinical practice guidelines published by DoD and the Department of Veterans Affairs outline the benefits of a multimodal approach to the evaluation and management mTBI.[27] There is increasing evidence that multimodal assessments that include evaluation of physical characteristics, such as balance and eye tracking, in addition to neurocognitive testing may provide a more effective approach to the evaluation and management of mTBI.[14,26,27] New research on brain imaging and biomarkers continues to elucidate the physiological signs of mTBI, with breakthroughs in finding hard-to-see microbleeds and white tissue damage[83,84] and identifying biomarker molecules associated with injured and recovering brain tissue.[85] A handful of biomarkers associated with moderate to severe TBI have been identified, and research is ongoing to determine whether they are also present and provide valuable clinical insights in mTBI.[85] While still a new field, these tests offer an objective assessment of a Service member's brain health following an injury that could contribute to a more comprehensive post-injury evaluation.

> **Finding 7:** There is evidence from academic research and from DoD that multimodal approaches including imaging, use of biomarkers, and physical diagnostic techniques may be more effective than NCATs alone in evaluating and managing mild traumatic brain injury.
>
> **Recommendation 7:** DoD should sustain and advance research to determine if a multimodal approach can be developed that is cost-effective and superior to NCAT testing alone in assessing and managing mild traumatic brain injury.

6.4 Test Reliability of ANAM4 and Its Individual Subtests

Given the normal fluctuation that occurs in the cognitive functions measured by ANAM4 and the relatively new application of ANAM to mTBI evaluation, there is need for research on the impact of depression, deployment, posttraumatic stress, acute stress, fatigue, and pain on subtest and overall test scores. This research should be conducted specifically in the military population, as Service members face unique stressors and experiences. This research may also yield new methods to evaluate the mental health of Service members not necessarily related to mTBI, allowing for improved diagnosis, documentation, and management of mental illness and post-traumatic stress.[64]

The heterogeneity of mTBI makes diagnosis and management challenging. The differences between blunt trauma-related mTBI and blast-related mTBI merit further research.[11] Currently, data suggest that there is little difference in the recovery process between the two injuries when evaluated using NCATs.[79,80] The large number of blast-related mTBI in recent conflicts highlights the need for state-of-the-art techniques to both assess and manage this condition as well as provide more effective treatment. Refinement of mTBI assessment tools such as ANAM4 and other clinical exams may allow clinicians to better understand the physiology of mTBI and monitor recovery. Identification of sensitive and specific biomarkers for TBI with diagnostic and prognostic properties would also be of significant value.

Another area of interest for the Subcommittee is practice effects. While practice effects for repeat administrations of ANAM4 have been demonstrated in healthy individuals, it appears that it is also present in individuals who have experienced mTBI, albeit at a lesser magnitude.[25,38,86] As researchers learn more about which cognitive functions, such as simple reaction time (SRT), tend to demonstrate deficits because of mTBI, it will be important to understand how practice effects influence scores on these subtests after serial administrations of ANAM4. Practice effects tend to improve the scores of Service members who have taken the test multiple times. If injured Service members' test scores improve after they have taken ANAM4 multiple times post-injury, the improvement may be a result of practice effects, rather than full recovery. This may result in an individual being returned to duty prematurely, putting them at risk for additional TBIs when their brains have not fully recovered. There is some evidence that suggests practice effects are diminished in individuals who have experienced mTBI.[25] If this is the case, manifestation of increased practice effects or improved scores may indicate recovery.

6.5 Research on Symptomatology of and Recovery from mTBI

Most individuals who experience mTBI recover within a few weeks; however, some individuals experience persistent symptoms or signs of mTBI. It is currently difficult to accurately correlate persistent symptoms with performance on ANAM4, as the test may not be able to discriminate between performance decrements related to chronic effects of mTBI or malingering.[16] Conversely, months after their injury individuals may report no symptoms but continue to score below their baseline on ANAM4. In these situations, comprehensive neuropsychological testing may be indicated to more precisely discern the potential roles of residual cognitive, psychological, and physical factors affecting ANAM4 test scores. In general, continued development and refinement of better tools and methods to discriminate between performance

decrements related to mTBI and other causes will allow clinicians to better manage patients by targeting interventions to the appropriate underlying causes.

> **Finding 8:** Individuals with persistent symptoms following mild traumatic brain injury are often found to have comorbidities such as post-traumatic stress, depression, sleep disturbances, pain, and anxiety. There is insufficient research on the impact of these comorbidities on ANAM4 test performance.
>
> **Recommendation 8:** DoD should conduct additional research to determine the effects of comorbidities on ANAM4 test performance.

With the conversion of more than 1.8 million ANAM4 test scores into an organized database, DoD has the opportunity to conduct extensive retrospective and prospective research. These data, along with additional patient outcome information, provide valuable longitudinal data on thousands of Service members. Analysis of these data in conjunction with available medical histories and symptom reports will allow researchers to investigate the impact of multiple mTBIs, long-term recovery, the effects of repeat testing, correlation of symptom resolution with test scores, comorbidities, lingering symptoms, and persistent low scores on ANAM. If a deidentified version of the data was made readily available to researchers, it would provide a valuable and cost-effective resource to leverage both civilian and military expertise to more rapidly advance the science of using NCATs in evaluating and managing mTBI.

> **Finding 9:** DoD has collected more than 1.8 million baseline, clinical, and other ANAM4 test results.
>
> **Recommendation 9:** DoD should make a deidentified version of these data available to civilian researchers to leverage those resources in accomplishing additional analyses

6.6 ANAM4 Test Score Interpretation Methodology

Although ANAM's technology allows for precise measurements of reaction time and other psychometric measures, interpretation of ANAM4 score results remains inconsistent. Methods for calculating reliable change, as well as interpreting change in score between baseline and post-injury test, vary widely.[71] In addition, the methodologies for comparing post-injury ANAM4 scores to baseline and normative data vary, as clinicians may set different definitions of impairment. For example, when comparing post-injury ANAM4 scores to a normative dataset, a clinician may classify a Service member as "impaired" if they score one standard deviation below the norm on one subtest, while others may classify a Service member as impaired if they score two standard deviations below the mean.[5] These differences lead to challenges in calculating the sensitivity and specificity of using individual baselines versus normative data, making accurate comparison of the two approaches difficult. Key areas for research, such as investigation of the best methodology for interpreting post-injury scores when pre-deployment baselines are available and identification of the best algorithms for interpreting post-injury scores when comparing to normative data, will aid in that endeavor. Researchers have also suggested that DoD "develop and evaluate clinical algorithms, with known false positive rates, for identifying and quantifying cognitive impairment following mTBI."[16]

When investigating practice effect, it will also be important to review which method is most accurate for interpreting changes in score on ANAM4 retests. Two methodologies that are currently used are the reliable change method and the regression-based change model.[71] A head-to-head comparison of the two methods would help determine the impact of practice effects and assess the reliability of ANAM4.[87] While these methods are currently widely used, some researchers argue that more sophisticated methods for interpreting change on NCATs should be developed. These may include refining the reliable change methodology to correct for practice effects and stratification of confidence intervals for change based on level of baseline performance.[16] Researchers have also suggested applying multivariate base rate analyses to the reliable change methodology to allow for quantification of the likelihood of showing one reliable change on one or more scores when multiple scores are considered simultaneously.

6.7 Test Environment and Administration

Testing environment has been identified as a factor potentially contributing to variation in NCAT testing results. Guidelines for administering ANAM4 are outlined in the ANAM4 User Manual, and clearly state that the testing environment be clean, quiet, comfortable, and free of distraction. The current policy of administering pre-deployment baseline testing in a group setting may not adhere to these standards, possibly resulting in Service members scoring lower when ANAM4 is administered that way. This belief is supported by the research of Moser, et al, who found that athletes score significantly lower on computerized neurocognitive tests when tests are administered in a group setting rather than individually.[28] Further study of the psychometric implications of completing the ANAM4 in group versus individual settings will contribute to determining the best approach to obtain more consistent and accurate baselines.

Other concerns include the effect of confusion or misunderstanding about the test or testing instructions on test scores. It is unclear whether low scores that occur because of confusion are highlighted by validity indicators or not.[60] If these low scores are not identified by the algorithms used to assess validity, it is possible that Service members who were confused by testing instructions will demonstrate lower ANAM4 baseline scores, thereby reducing the accuracy of baseline comparison to post-injury test scores if they sustain an mTBI.

> **Finding 10:** DoD currently administers ANAM4 baseline tests in group settings; however, research indicates that administering computerized neurocognitive tests in a group setting may affect an individual’s test score.[28]
>
> **Recommendation 10:** DoD should determine whether and to what extent the group testing environment affects ANAM4 baseline tests scores as compared to individual ANAM4 testing.

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7. APPENDICES

APPENDIX A: LETTER OF REQUEST

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND READINESS

JUL 25 2014

MEMORANDUM FOR PRESIDENT, DEFENSE HEALTH BOARD

SUBJECT: Request to Review the Scientific Evidence of Using Population Normative Values for Post-Concussive Computerized Neurocognitive Assessments

As post-concussive neurocognitive assessment continues to evolve, the scientific, military, and sports communities have raised questions regarding the utility of using baseline assessments for post-injury comparison, versus using population normative values, to define injury-related cognitive deficits and help inform return-to-duty and return-to-play decisions. The Department currently collects computerized, pre-deployment baseline neurocognitive assessment data using the Automated Neuropsychological Assessment Metrics 4 (ANAM4). Baseline ANAM4 data are available for retrieval and comparison to post-injury ANAM4 assessment results should a Service member experience a concussive injury. Since July 2007, the Department completed more than 1.5 million pre-deployment baseline tests and executed 26,524 post-injury comparison assessments.

The Military Services have raised concerns about the utility and logistics of continuing to collect pre-deployment baseline neurocognitive tests because emerging scientific evidence suggests that before and after comparative testing using baselines may be no more effective than using relevant population normative values for the detection of cognitive deficits associated with the concussion. Therefore, I request that the Defense Health Board (DHB) examine the state-of-the-science on neurocognitive assessment testing, and recommend the DHB evaluation consider the following questions:

1) Does the current state-of-the science demonstrate a continued need for baseline computerized neurocognitive tests to make return-to-duty/play determinations?

2) Is the current dataset of military relevant normative values for the ANAM4 (sample size 107,000) an adequately sized population to generate age, gender, education, and rank-matched military normative values, or should a larger dataset be implemented for the norms?

3) Are population normative values (assuming an adequate number and military-relevant demographic profile) as scientifically sound as pre-deployment baseline tests for reliably detecting post-concussive neurocognitive deficits (within the limitations of ANAM4) for return-to-duty decision making and prognosis?

4) Is there any utility to expanding the use of neurocognitive assessment testing of military populations beyond the deployment cycle (pre-deployment, post-injury, post-deployment)?

5) Is any additional direction for future research in neurocognitive assessment testing needed to improve protection of the fighting force?

6) What is the cost benefit of performing baseline testing for the Military Services in a fiscally constrained environment, when logistics, contracts, personnel, and equipment sustainment are taken into consideration?

The point of contact for this action is Ms. Elizabeth Fudge, Defense Health Agency, Health Care Operations Directorate. Ms. Fudge may be reached at (703) 681-8295 or elizabeth.fudge@dha.mil.

JWright

Jessica L. Wright

2

Appendix B: Terms of Reference

Defense Health Board
Review of Scientific Evidence of Using Population Normative Values for Post-Concussive Neurocognitive Assessments

TERMS OF REFERENCE

These terms of reference establish the objectives for the Defense Health Board's (DHB) examination of the state of the science in neurocognitive assessment testing in evaluating mild traumatic brain injury (mTBI, or concussion) and the effectiveness of the Department of Defense's (DoD's) current testing program. The terms outline the scope of the Board's examination as well as the Board's methodology for responding to DoD's request.

Mission Statement: The DHB will conduct a comprehensive review of the Automated Neuropsychological Assessment Metrics 4 (ANAM4) neurocognitive assessment testing in the evaluation of mTBI and offer recommendations regarding the appropriateness of using normative values, as opposed to individual baseline tests, when making return-to-duty decisions; the adequacy of the current normative dataset; the use of neurocognitive testing beyond the normal deployment cycle; and future research.

Issue Statement: On July 25, 2014, the Under Secretary of Defense for Personnel and Readiness requested the DHB review the scientific evidence of using population normative values for post-concussive computerized neurocognitive testing. The stated premise for this request was that emerging scientific evidence suggests that using individual baseline neurocognitive assessments for post-injury comparison may be no more effective than using population normative values to define injury-related cognitive deficits and inform return-to-duty and return-to-play decisions. Consequently, the Military Services have expressed concern about the utility of continuing to collect pre-deployment baseline neurocognitive test data. Computerized, pre-deployment baseline neurocognitive assessment testing using the ANAM4 is currently performed on Service members within 12 months before deployment. Baseline ANAM4 data are available for retrieval and comparison to post-injury ANAM4 assessment results should a Service member experience mTBI. As of July 25, 2014, the Department completed more than 1.5 million pre-deployment baseline tests and executed 26,524 post-injury comparison assessments since July 2007.

Objectives and Scope: The DHB will address the following in its report:

1. Review the current state of the science to determine whether there is a continued need for individual baseline neurocognitive testing, as one element of making return-to-duty/play determinations;

2. Determine whether the current dataset of military relevant normative values for the ANAM4 is adequately sized to generate age, gender, education and rank-matched military normative values;

3. Determine whether population normative values, as one element, are as scientifically sound as pre-deployment baseline tests for reliably detecting post-concussive neurocognitive deficits, as one element for return-to-duty decisions and the value of ANAM4 in making a prognosis;

4. Determine whether expanding the use of computerized ANAM4 neurocognitive assessment testing of military populations in addition to the deployment cycle (pre-deployment, post-injury, post-deployment), such as in garrison, is of value;

5. Identify directions for future research in computerized ANAM4 neurocognitive assessment testing to protect the fighting force and to improve the effectiveness of mTBI assessment, treatment, rehabilitation and disposition; and

6. Compare the cost and benefits of performing baseline testing in the Military Services when logistics, contracts, personnel, and equipment sustainment are considered.

Methodology: The Neurological/Behavioral Health Subcommittee will meet regularly to review the literature, receive briefings, and conduct site visits as needed. Using the information from these research activities, the Subcommittee will develop findings and recommendations based on the current state of neuroscience. The members will present their preliminary findings and recommendations to the DHB for consideration and deliberation. The DHB will deliberate the findings, during which time members may propose additional recommendations, and vote on these collective recommendations in an open public session.

Deliverable: The DHB will deliberate the final findings and recommendations presented by the Subcommittee in 2015 and produce the final report immediately following for presentation to the Department. The Subcommittee will provide progress updates to the Board at each DHB meeting before then.

Membership: The Neurological/Behavioral Health Subcommittee members will conduct the primary investigation and will consult subject matter experts as needed.

Support:

1. The DHB office will provide any necessary administrative, analytical, research, and logistical support for the Subcommittee and Board.

2. Funding for this review is included in the DHB operating budget.

APPENDIX C: ANAM4 TBI TEST DESCRIPTIONS

Demographics Module
The demographics module allows users to enter a wide variety of information including name, age, gender, ethnicity, medical diagnosis, medications, and additional comments that the researcher or clinician finds useful.

TBI Questionnaire
The TBI Questionnaire is designed to assess injury history and related symptomatology.

Sleep Scale
The ANAM sleepiness scale has been designed to provide a state and/or trait assessment of energy-fatigue level. This test permits self-assessment of the user's sleep/fatigue state (and/or trait). The user is presented with seven different statements of alertness/sleepiness ranging from "feeling very alert, wide awake, and energetic" to "Very sleepy and cannot stay awake much longer." The user is instructed to select the one statement that best matches the current state.

Mood Scale II – Revised
The Moodscale2-R is designed to assess either mood state of trait in participants in six subcategories that include Vigor (high energy-level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low-energy level), and Anxiety (anxiety level).

This test permits self- assessment of the user's mood state in seven categories: Vigor (high energy-level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low-energy level), and Anxiety (anxiety level), and a new subcategory of Restlessness (motor agitation). The user is presented with a scale of numbered blocks ranging from 0 to 6, with "0" having the verbal anchor "Not at all," the midpoint "3" labeled "Somewhat" and "6" labeled "Very Much." The user is presented a series of adjectives, each adjective contributing to one of the mood categories, and is instructed to select the box/number that best represents the current state with respect to the presented adjective.

Simple Reaction Time
The results of this test are used as an index of visuo-motor response timing.

This test measure simple reaction time by presenting the user with a series of " * " symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.

Code Substitution – Learning
Results of this test are used as an index of visual search, sustained attention, and encoding.

In this test the user must compare a displayed digit-symbol pair with a set of defined digit-symbol pairs, or the *key*. The user presses the designated buttons to indicate whether the pair in question represents a correct or incorrect mapping relative to the key. In the Learning phase (simultaneous presentation mode), the defined pairs are presented on the screen along with the

digit-symbol pair in question. In the Delayed Memory test (to follow later in the battery) the comparison stimuli are again presented individually without the key.

Procedural Reaction Time
This test measures the reaction time and processing efficiency associated with following a simple set of mapping rules.

There are three possible blocks of trials for this test. In the Basic Block, the user is presented with a number constructed on the display using a large dot matrix (either a 2, 3, 4, or 5). The user is instructed to press on designated button for a "low" number (2 or 3) and another designated button for a "high" number (4 or 5).

Matching to Sample
Results of this test are used as an index of spatial processing and visuo-spatial working memory.

During this test the user views a pattern produced by eight shaded cells in a 4 x 4 sample grid. The sample is then removed and two comparison patterns are displayed side by side. One grid is identical to the sample grid and the other grid differs by one shaded cell. The user is instructed to press a designated button to select the grid that matches the sample.

Mathematical Processing
Results of this test are used as an index of basic computational skills, concentration, and working memory.

During this task, an arithmetic problem involving three single-digit numbers and two operators is displayed (e.g., "5 – 2 + 3 ="). The user presses buttons to indicate whether the answer to the problem is less than five or greater than five.

Code Substitution – Delayed (Recognition)
Results of this test are used as an index of delayed memory.

In this test the user must compare the displayed digit-symbol pair with the digit-symbol pairs, or key, presented during the Code Substitution – Learning test. The user presses designated buttons to indicate whether the pair in question represents a correct or incorrect mapping relative to the key.

Simple Reaction Time
Results of this test are used as an index of visuo-motor response timing.

This is a repeat of the Simple Reaction Time test presented earlier in the battery. This test measures simple reaction time by presenting the user with a series of "*" symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.

Adapted from: C-SHOP (2007). ANAM4 TBI: User Manual. Center for the Study of Human Operator Performance, University of Oklahoma, Norman, OK. Pages 15-18.[50]

Appendix C References

50. C-Shop. ANAM4 TBI: User Manual. Norman, OK.: Center for the Study of Human Operator Performance, University of Oklahoma; 2007.

Appendix D: Breakdown of Total ANAM4 Test Results by Year and Reason

Through 23-JUL-15	Pre-D	Post-D	Clin Eval	Injury	Recovery	Unspecified	
Percentage	93.74%	3.01%	1.29%	0.26%	0.03%	1.67%	
Sum of Count	**Column Labels**						
Period/Service	**Pre-D**	**Post-D**	**Clinical**	**Injury**	**Recovery**	**Unspecified**	**Total**
2007 Q2	**0**	**0**	**0**	**0**	**0**	**335**	**335**
Army	0	0	0	0	0	335	335
2007 Q3	**12,589**	**27**	**20**	**1**	**2**	**242**	**12,881**
Air Force	2	0	0	1	0	2	5
Army	12,538	27	18	0	2	239	12,824
Non Military	49	0	2	0	0	1	52
2007 Q4	**22,611**	**3,853**	**118**	**9**	**7**	**3,713**	**30,311**
Air Force	268	148	1	0	0	6	423
Army	22,324	3,705	116	9	7	3,701	29,862
Non Military	19	0	1	0	0	6	26
2008 Q1	**10,660**	**93**	**169**	**4**	**0**	**116**	**11,042**
Air Force	1,246	2	155	1	0	31	1,435
Army	9,370	91	14	3	0	83	9,561
Marine Corps	4	0	0	0	0	0	4
Navy	29	0	0	0	0	0	29
Non Military	11	0	0	0	0	2	13
2008 Q2	**7,127**	**1,228**	**316**	**5**	**4**	**314**	**8,994**
Air Force	654	5	199	0	0	8	866
Army	6,461	1,223	116	5	4	306	8,115
Marine Corps	1	0	0	0	0	0	1
Non Military	11	0	1	0	0	0	12
2008 Q3	**30,800**	**736**	**214**	**20**	**2**	**1,051**	**32,833**
Air Force	1,780	60	13	2	0	53	1,908
Army	25,331	666	173	17	2	858	27,057
Coast Guard	0	0	1	0	0	0	1
Marine Corps	3,237	9	25	1	0	115	3,387
Navy	390	1	1	0	0	17	409
Non Military	62	0	1	0	0	8	71
2008 Q4	**50,341**	**10,996**	**446**	**104**	**10**	**1,489**	**63,387**
Air Force	2,626	247	23	7	0	55	2,958
Army	45,936	10,743	403	94	9	1,358	58,544
Marine Corps	1,497	4	8	3	1	69	1,582
Navy	198	0	7	0	0	3	208
Non Military	84	2	5	0	0	4	95
2009 Q1	**70,057**	**4,161**	**569**	**22**	**9**	**2,042**	**76,861**
Air Force	5,931	47	31	0	1	141	6,151
Army	37,410	3,939	342	15	4	1,022	42,733
Coast Guard	4	0	1	0	0	0	5
Marine Corps	22,377	134	184	7	4	742	23,448
Navy	4,242	39	10	0	0	131	4,422
Non Military	93	2	1	0	0	6	102
2009 Q2	**78,888**	**2,707**	**278**	**14**	**4**	**1,622**	**83,513**
Air Force	6,759	37	26	0	3	68	6,893
Army	58,381	2,614	203	9	1	1,321	62,529
Coast Guard	143	0	0	0	0	0	143
Marine Corps	9,766	43	44	5	0	153	10,011
Navy	3,757	11	5	0	0	75	3,848
Non Military	82	2	0	0	0	5	89
2009 Q3	**69,605**	**1,477**	**311**	**22**	**22**	**1,076**	**72,513**
Air Force	5,263	10	3	0	0	42	5,318
Army	50,159	1,433	271	19	21	816	52,719
Coast Guard	35	0	0	0	0	0	35
Marine Corps	11,324	29	37	3	1	183	11,577
Navy	2,745	5	0	0	0	35	2,785
Non Military	79	0	0	0	0	0	79

Adapted from ANAM Program Office, 2015.[5]

Period/Service	Pre-D	Post-D	Clinical	Injury	Recovery	Unspecified	Total
2009 Q4	**64,196**	**2,886**	**484**	**12**	**1**	**1,133**	**68,712**
Air Force	13,988	134	71	1	0	179	14,373
Army	41,511	2,714	295	11	1	832	45,364
Coast Guard	146	0	0	0	0	0	146
Marine Corps	5,578	29	109	0	0	57	5,773
Navy	2,811	8	8	0	0	59	2,886
Non Military	162	1	1	0	0	6	170
2010 Q1	**79,000**	**479**	**583**	**25**	**7**	**1,537**	**81,631**
Air Force	16,008	85	47	4	0	295	16,439
Army	43,480	349	328	16	5	876	45,054
Coast Guard	2	0	1	0	0	0	3
Marine Corps	15,472	35	186	3	2	324	16,022
Navy	3,845	9	19	2	0	37	3,912
Non Military	193	1	2	0	0	5	201
2010 Q2	**75,794**	**838**	**791**	**73**	**74**	**1,367**	**78,937**
Air Force	18,580	53	95	6	1	394	19,129
Army	41,423	747	581	22	5	753	43,531
Coast Guard	200	1	0	0	0	2	203
Marine Corps	11,775	30	98	40	68	135	12,146
Navy	3,647	6	13	4	0	76	3,746
Non Military	169	1	4	1	0	7	182
2010 Q3	**75,088**	**565**	**877**	**629**	**144**	**1,033**	**78,336**
Air Force	16,170	45	89	16	2	236	16,558
Army	45,745	489	654	160	17	682	47,747
Coast Guard	102	0	0	0	0	1	103
Marine Corps	8,882	21	118	429	114	80	9,644
Navy	3,788	9	14	21	11	24	3,867
Non Military	401	1	2	3	0	10	417
2010 Q4	**68,292**	**795**	**894**	**490**	**37**	**819**	**71,327**
Air Force	13,975	53	35	5	2	208	14,278
Army	37,746	693	675	132	8	473	39,727
Coast Guard	21	0	0	0	0	0	21
Marine Corps	10,882	15	164	334	24	65	11,484
Navy	4,449	27	16	13	3	36	4,544
Non Military	1,219	7	4	6	0	37	1,273
2011 Q1	**93,010**	**4,948**	**693**	**499**	**33**	**1,461**	**100,644**
Air Force	15,437	53	17	8	1	321	15,837
Army	54,161	4,729	384	168	8	856	60,306
Coast Guard	254	0	0	0	0	1	255
Marine Corps	15,875	119	253	304	24	145	16,720
Navy	5,241	37	28	15	0	62	5,383
Non Military	2,042	10	11	4	0	76	2,143
2011 Q2	**71,386**	**6,190**	**776**	**483**	**46**	**851**	**79,732**
Air Force	13,617	51	25	5	1	221	13,920
Army	41,057	6,040	371	160	13	473	48,114
Coast Guard	103	0	0	0	0	0	103
Marine Corps	10,174	64	343	305	31	85	11,002
Navy	4,953	29	33	11	1	42	5,069
Non Military	1,482	6	4	2	0	30	1,524
2011 Q3	**67,097**	**3,535**	**1,400**	**331**	**61**	**910**	**73,334**
Air Force	13,965	42	16	9	1	238	14,271
Army	37,321	3,426	910	90	38	466	42,251
Coast Guard	105	0	0	0	0	0	105
Marine Corps	9,609	33	425	225	19	95	10,406
Navy	3,496	24	37	7	3	43	3,610
Non Military	2,601	10	12	0	0	68	2,691

Period/Service	Pre-D	Post-D	Clinical	Injury	Recovery	Unspecified	Total
2011 Q4	**54,558**	**1,779**	**869**	**316**	**24**	**680**	**58,226**
Air Force	11,239	48	15	14	0	222	11,538
Army	27,589	1,626	584	157	9	280	30,245
Coast Guard	112	0	0	0	0	0	112
Marine Corps	9,887	27	244	134	13	65	10,370
Navy	2,721	68	22	9	2	32	2,854
Non Military	3,010	10	4	2	0	81	3,107
2012 Q1	**63,447**	**2,674**	**2,352**	**187**	**27**	**860**	**69,547**
Air Force	12,349	45	14	8	1	114	12,531
Army	33,224	2,525	670	101	10	455	36,985
Coast Guard	135	0	0	0	0	0	135
Marine Corps	10,066	47	1,524	62	16	83	11,798
Navy	4,236	39	141	15	0	54	4,485
Non Military	3,437	18	3	1	0	154	3,613
2012 Q2	**57,535**	**880**	**1,817**	**333**	**12**	**853**	**61,430**
Air Force	11,082	33	13	20	0	117	11,265
Army	31,082	767	716	240	11	484	33,300
Coast Guard	139	0	0	0	0	1	140
Marine Corps	9,020	22	1,035	62	1	50	10,190
Navy	2,965	39	42	8	0	11	3,065
Non Military	3,247	19	11	3	0	190	3,470
2012 Q3	**62,685**	**860**	**1,081**	**435**	**15**	**855**	**65,931**
Air Force	11,547	28	23	15	0	113	11,726
Army	39,023	763	375	369	13	527	41,070
Coast Guard	87	0	1	0	0	1	89
Marine Corps	5,860	10	639	45	2	12	6,568
Navy	2,960	40	32	5	0	10	3,047
Non Military	3,208	19	11	1	0	192	3,431
2012 Q4	**62,948**	**532**	**1,425**	**200**	**9**	**985**	**66,099**
Air Force	8,872	43	6	7	0	120	9,048
Army	40,147	419	372	124	4	643	41,709
Coast Guard	17	0	0	0	0	0	17
Marine Corps	8,148	20	975	59	5	16	9,223
Navy	2,314	24	66	10	0	17	2,431
Non Military	3,450	26	6	0	0	189	3,671
2013 Q1	**62,132**	**1,095**	**1,228**	**87**	**15**	**972**	**65,529**
Air Force	12,721	52	187	11	0	138	13,109
Army	36,658	985	426	60	10	587	38,726
Coast Guard	114	0	0	0	0	0	114
Marine Corps	6,587	20	575	13	4	11	7,210
Navy	2,481	15	32	3	0	24	2,555
Non Military	3,571	23	8	0	1	212	3,815
2013 Q2	**58,119**	**284**	**558**	**60**	**13**	**706**	**59,740**
Air Force	10,335	33	97	9	0	116	10,590
Army	34,167	194	405	41	11	420	35,238
Coast Guard	75	0	0	0	0	0	75
Marine Corps	8,902	14	38	7	1	43	9,005
Navy	2,175	33	14	3	1	15	2,241
Non Military	2,465	10	4	0	0	112	2,591
2013 Q3	**52,872**	**217**	**1,372**	**132**	**6**	**652**	**55,251**
Air Force	11,040	34	17	14	0	120	11,225
Army	29,561	153	259	111	6	310	30,400
Coast Guard	69	0	0	0	0	0	69
Marine Corps	7,397	12	961	2	0	22	8,394
Navy	2,187	7	131	5	0	22	2,352
Non Military	2,618	11	4	0	0	178	2,811

Period/Service	Pre-D	Post-D	Clinical	Injury	Recovery	Unspecified	Total
2013 Q4	**47,433**	**221**	**942**	**47**	**8**	**587**	**49,238**
Air Force	9,772	41	12	17	0	156	9,998
Army	26,444	139	217	29	8	302	27,139
Coast Guard	37	0	0	0	0	1	38
Marine Corps	6,768	8	671	0	0	5	7,452
Navy	1,997	19	35	0	0	12	2,063
Non Military	2,415	14	7	1	0	111	2,548
2014 Q1	**48,216**	**237**	**1,015**	**9**	**5**	**458**	**49,940**
Air Force	11,103	36	31	2	2	139	11,313
Army	25,023	153	224	7	2	165	25,574
Coast Guard	102	0	0	0	0	0	102
Marine Corps	7,532	26	676	0	1	9	8,244
Navy	2,007	8	82	0	0	17	2,114
Non Military	2,449	14	2	0	0	128	2,593
2014 Q2	**50,585**	**482**	**670**	**30**	**3**	**522**	**52,292**
Air Force	9,957	50	20	6	0	170	10,203
Army	27,569	380	281	20	2	244	28,496
Coast Guard	76	0	0	0	0	0	76
Marine Corps	7,843	28	341	3	0	6	8,221
Navy	2,945	10	26	1	1	12	2,995
Non Military	2,195	14	2	0	0	90	2,301
2014 Q3	**43,617**	**142**	**657**	**37**	**6**	**439**	**44,898**
Air Force	11,575	39	67	5	1	182	11,869
Army	23,102	89	381	29	5	218	23,824
Coast Guard	86	0	0	0	0	0	86
Marine Corps	6,139	8	195	2	0	9	6,353
Navy	1,752	2	12	1	0	11	1,778
Non Military	963	4	2	0	0	19	988
2014 Q4	**38,908**	**225**	**357**	**76**	**2**	**454**	**40,022**
Air Force	9,129	45	51	6	1	238	9,470
Army	23,307	157	264	67	1	187	23,983
Coast Guard	10	0	0	0	0	0	10
Marine Corps	3,559	7	36	2	0	1	3,605
Navy	2,303	6	2	1	0	17	2,329
Non Military	600	10	4	0	0	11	625
2015 Q1	**43,125**	**131**	**316**	**18**	**4**	**377**	**43,971**
Air Force	9,413	27	9	3	0	80	9,532
Army	23,088	92	298	12	4	275	23,769
Coast Guard	12	0	0	0	0	0	12
Marine Corps	8,326	6	5	3	0	4	8,344
Navy	1,707	3	3	0	0	7	1,720
Non Military	579	3	1	0	0	11	594
2015 Q2	**33,481**	**134**	**186**	**11**	**0**	**240**	**34,052**
Air Force	7,335	20	7	5	0	41	7,408
Army	19,103	104	164	4	0	176	19,551
Coast Guard	9	0	0	0	0	0	9
Marine Corps	4,563	4	12	1	0	3	4,583
Navy	1,888	4	3	1	0	10	1,906
Non Military	583	2	0	0	0	10	595
Grand Total	**1,726,202**	**55,407**	**23,784**	**4,721**	**612**	**30,751**	**1,841,489**

Appendix D References

5. Meyers J. Briefing to the Neurological/Behavioral Health Subcommittee. September 28, 2015.

APPENDIX E: PROPOSED RESEARCH HIGHLIGHTED IN LITERATURE

Area of Interest	Recommendation	Source
Impact of baselines on post-injury mTBI management	If multidimensional clinical assessment was used following an mTBI, does the addition of baseline pre-injury test scores contribute in a meaningful way to medical management and return-to-duty decisions?	Dr. Grant Iverson[87]
	Assess the reliability and validity of a baseline versus no baseline model of CNT assessment when measuring the acute effects of sports related concussion.	Resch et al 2013[24]
	Conduct programmatic research relating to the strengths and limitations of baseline testing for improving the accuracy of neuropsychological assessment and determining whether improved accuracy contributes to improved management of this injury in athletes.	Iverson and Schatz, 2015[16]
ANAM Score Interpretation	What is the best methodology for interpreting post-concussion test scores when baseline (i.e., pre-deployment) test scores are available?	Dr. Grant Iverson[87]
	What are the best clinical algorithms for interpreting ANAM scores following a mild traumatic brain injury in the absence of baseline pre-injury test scores?	Dr. Grant Iverson[87]
	Is having pre-deployment ANAM scores superior to not having these scores when interpreting scores following a mild traumatic brain injury?	Dr. Grant Iverson[87]
	Is the reliable change methodology or regression-based change models preferred for interpreting retest scores on the ANAM?	Dr. Grant Iverson[87]
	Develop and evaluate more sophisticated methods for interpreting change on cognitive testing (e.g., refinements of the reliable change methodology, such as correction for practice and stratification of confidence intervals for change based on level of baseline performance; and use of standardized regression models). Apply multivariate base rate analyses to the reliable change methodology to quantify the likelihood of showing one or more reliable change scores when multiple change scores are considered simultaneously.	Iverson and Schatz, 2015[16]
	Develop and evaluate clinical algorithms, with known false positive rates, for	Iverson and Schatz, 2015[16]

Area of Interest	Recommendation	Source
	identifying and quantifying cognitive impairment following concussion.	
ANAM Test/Sub-Test Sensitivity	Is the ANAM sensitive to cognitive difficulties associated with depression, pain, acute traumatic stress, or some combination of these factors?	Dr. Grant Iverson[87]
	Which ANAM subtests are most sensitive to cognitive deficits in those with moderate or severe TBIs after 1 year of recovery time?	Dr. Grant Iverson[87]
Impact of Devices/Technology on ANAM Scores	What are the psychometric implications of completing the ANAM on different devices?	Dr. Grant Iverson[87]
Test Setting/Administration	What are the psychometric implications of completing the ANAM in individual or group settings?	Dr. Grant Iverson[87]
	Examine how confusion or misunderstanding on the part of the subject, regarding the test instructions or procedures, influences the probability of being flagged by a validity indicator.	Iverson and Schatz, 2015[16]
	Establish guidelines for "best practices" in the administration of CNTs across multiple sports, age groups and levels of competition.	Resch et al 2013[24]
Comparison of ANAM to Other Tests	Does the ANAM have comparable or superior reliability and clinical usefulness as other brief computerized cognitive assessment batteries?	Dr. Grant Iverson[87]
	Further demonstrate and report the psychometric properties of each CNTs in the assessment of sports related concussion through prospective studies of adult and youth athletes.	Resch et al 2013[24]
	Investigate the psychometric evidence for equivalence of alternate forms provided by each CNT.	Resch et al 2013[24]
Timing of testing	Investigate the added value of CNTs compared to traditional neuropsychological tests as measures of cognitive recovery at sequential time points following injury.	Resch et al 2013[24]
	Determine if cognitive functioning, assessed in the first 72 hours post injury, has prognostic value for predicting typical versus slow recovery.	Iverson and Schatz 2015[16]
	Pursue analogue malingering studies to	Iverson and Schatz 2015[16]

Area of Interest	Recommendation	Source
	better understand how people under-perform on computerized testing.	
Test/Re-test Effects	Evaluate and improve, if possible, the test–re-test reliability of traditional and computerized cognitive tests. Determine if there are differences in the magnitude of practice effects based on the domain of cognitive functioning assessed and whether the test is paper–pencil or computerized.	Iverson and Schatz 2015[16]
Sources of Error	Investigate additional sources of random and systematic error that may influence CNT performance.	Resch et al 2013[24]
Blast Injuries and Multiple Concussions	Continued study of combat related blast concussions is important to our efforts to quickly and safely return service members to duty, treat persistent concussion symptoms, and avoid long-term sequel and CTE.	Kelly et al 2012[60]
	[There are] [l]ongitudinal bodies of data currently available from which to draw conclusions regarding the impact of multiple concussions during combat.	Kelly et al 2012[60]

Appendix E References

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Appendix F: Meetings and Briefings

October 2, 2014

On this teleconference members discussed the tasking and a potential way forward. There were no briefings at this meeting.

December 18, 2014

On this teleconference members discussed the tasking, the Automated Neuropsychological Assessment Metrics (ANAM) program, and ANAM data analyses with subject matter experts.

Subject matter experts in attendance:

- Ms. Kathy Helmick, Deputy Director, Defense and Veterans' Brain Injury Center
- COL Sidney Hinds, Director, Defense and Veterans' Brain Injury Center
- Dr. Donald Marion, Senior Clinical Consultant, Clinical Affairs, Defense and Veterans' Brain Injury Center
- Dr. Mark Kelly, Program Director, Postdoctoral Fellowship in Clinical Neuropsychology, Walter Reed National Military Medical Center

February 17, 2015

On this teleconference members discussed the way ahead and reviewed their Terms of Reference and Guiding Principles. There were no briefings at this meeting.

March 11, 2015
Falls Church, Virginia

Members met with subject matter experts to discuss the ANAM4 database and testing as well as evaluation, treatment, and management of mTBI. Members also reviewed their Terms of Reference and Guiding Principles, and discussed the way ahead.

Subject matters in attendance:

- Dr. John Meyers, Neuropsychologist, ANAM Program Director/Chief Neurocognitive Assessment Branch, Rehabilitation and Reintegration Division; Headquarters, Department of the Army (HQDA), Office of the Army Surgeon General
- MAJ Robert Parish, Medical Service Corps Deputy Chief, Department of Behavioral Health Officer in Charge, mild Traumatic Brain Injury (mTBI) Clinic Clinical Neuropsychologist
- LCDR Steven Porter, Clinical Neuropsychologist, Midshipmen Development Center, United States Naval Academy
- Dr. Michael Russell, Director, Veterans Integrated Service Network 17 Center of Excellence for Research on Returning War Veterans
- CAPT Jack Tsao, Director of Traumatic Brain Injury Programs for the U.S. Navy Bureau of Medicine and Surgery; Professor of Neurology, Uniformed Services University of the Health Sciences; Fellow of the American Academy of Neurology

April 27, 2015

On this teleconference members discussed issues in neurocognitive assessment of mTBI with subject matter experts. Members also reviewed the draft report and future briefings needed.

Subject matter experts in attendance:
- Dr. Grant Iverson, Director, Sports Concussion Program, Massachusetts General Hospital for Children; Director, Neuropsychology Outcome Assessment Laboratory, Department of Physical Medicine and Rehabilitation, Harvard Medical School
- Dr. Philip Schatz, Director Behavioral Neurosciences Program, Saint Joseph's University

May 26, 2015

On this teleconference members discussed issues in neurocognitive assessment of mTBI with subject matter experts. Members also reviewed the draft report outline.

Subject matter experts in attendance:
- Dr. Alison Cernich, Director, National Center for Medical Rehabilitation Research at the National Institute of Child Health and Human Development
- Dr. Michael McCrea, Professor of Neurosurgery and Neurology; Director of Brain Injury Research, Medical College of Wisconsin

July 9, 2015

On this teleconference members reviewed and edited the draft outline and report. There were no briefings at this meeting.

July 23, 2015

On this teleconference members reviewed and edited the draft report. There were no briefings at this meeting.

August 31, 2015

On this teleconference members discussed computerized neurocognitive testing with a subject matter expert. Members also reviewed and edited the draft report.

Subject matter expert in attendance:
- Dr. Wayne Chappelle, Consultant to the Surgeon General, Aeromedical Clinical Psychology, U.S. Air Force School of Aerospace Medicine

September 28, 2015

On this teleconference members discussed the ANAM4 database and baseline testing with subject matter experts. Members also reviewed and edited the draft report.

Subject matter experts in attendance:

- Dr. John Meyers, Neuropsychologist, ANAM Program Director/Chief Neurocognitive Assessment Branch, Rehabilitation and Reintegration Division, HQDA, Office of the Army Surgeon General
- Dr. Stephanie Maxfield-Panker, Acting TBI Program Director, Office of the Army Surgeon General, Rehabilitation and Reintegration Division

October 19, 2015

On this teleconference members discussed the quality of computerized neurocognitive assessments with subject matter experts. Members also reviewed and edited the draft report.

Subject matter experts in attendance:

- Dr. David Cifu, National Director of Physical Medicine &Rehabilitation (PM&R) Program Office, Veterans Health Administration; Chairman and Herman J. Flax, M.D. Professor Department of PM&R, Virginia Commonwealth University
- Dr. Chris Giza, Professor of Pediatric Neurology and Neurosurgery, UCLA Brain Injury Research Center

October 26, 2015

On this teleconference members reviewed and edited the draft findings and recommendations. No subject matter experts attended this teleconference.

November 9, 2015
Defense Health Board Meeting
MacDill Air Force Base, Florida

Dr. David Hovda, Subcommittee chair, presented the deliberative pre-decisional draft of the report.

Appendix G: Acronyms

AMEDD	United States Army Medical Department
ANAM4	Automated Neuropsychological Assessment Metrics 4
CNAD	Computerized Neurocognitive Assessment Device
CNT	Computerized Neurocognitive Test
C-SHOP	Center for the Study of Human Operator Performance
DANA	Defense Automated Neurobehavioral Assessment
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DHB	Defense Health Board
DoD	Department of Defense
DoDI	Department of Defense Instruction
DVBIC	Defense and Veterans' Brain Injury Center
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
MACE	Military Acute Concussion Evaluation
mTBI	Mild Traumatic Brain Injury
NCAT	Neurocognitive Assessment Tool
NDAA	National Defense Authorization Act
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PRT	Procedural Reaction Time
PTSD	Post-Traumatic Stress Disorder
SRT	Simple Reaction Time
TBI	Traumatic Brain Injury
USASOC	United States Army Special Operations Command
USD(R&R)	Under Secretary of Defense, Personnel and Readiness
USNA	United States Naval Academy

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